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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

AUGUST, 1926

ORIGINAL ARTICLES.

LYMPHOBLASTOMA.

Aspects Concerning Abdominal Lesions, Especially their Production of Early Symptoms.

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and

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Boston.

(From the Medical Services of the Collis P. Huntington Memorial Hospital of Harvard University and the Massachusetts General Hospital.)

Introduction and Material Studied.—Lesions of the various types of lymphoblastoma are well known to develop within the abdomen as a late manifestation of disease. They are apt to be thought of as first appearing in the neck. It has been commented upon but little that the abdomen is often the seat of the initial lesion or that the resulting symptoms frequently are prominent early. Hodgkin, in 1832, and Wilks, in 1865, in their classical papers on Enlargement of Lymph Nodes, noted the involvement of lymphoid tissue within the abdomen, and were careful to observe the effects of pressure on surrounding structures at autopsy. Symmers,[1] in his paper on Hodgkin's disease, which is considered by some a form of lymphoblastoma, has indicated clearly that preponderating enlargement of the cervical nodes is not the rule and that involvement of tissue within the abdomen is common and often the place where the disease originally starts. Lesions of lymphatic leukemia,

its aleukemic form or pseudoleukemia and lymphosarcoma, which are the other chief forms of lymphoblastoma, are also commonly found in the abdomen. The latter two types involve the gastrointestinal tract much more often than does Hodgkin's disease, but all frequently create masses within the abdomen.

The information presented here concerning certain aspects of lymphoblastoma within the abdomen has been obtained from a study of 477 cases, exclusive of the form known as lymphatic leukemia. The data on somewhat less than half the cases have been obtained from records compiled by others, while the rest have been obtained by one of us. The diagnosis was established in 85 per cent of these 477 cases (401 dead, 76 living) by histologic examination of tissue and in those having early abdominal lesions an even greater percentage had the diagnosis confirmed in this manner.

Facts concerning age and sex incidence and duration of lymphoblastoma and the influence upon it of irradiation and surgery for these 477 cases have been presented elsewhere.[2] During this study it became strikingly apparent that the patients frequently complained, early in the course of their disease, of symptoms referable to abdominal lesions. It is the purpose of the present communication to record in a general manner the nature and incidence of such symptoms together with certain other aspects presented by patients with lymphoblastoma within the abdomen, but whose disease involved other and often many parts of the body in nearly all instances. Cases of lymphatic leukemia are excluded only because they have been studied separately. The abdominal manifestations of this condition are similar to those of the other forms of lymphoblastoma and do occur with great frequency as early symptoms, even of a sort suggesting colitis, gallbladder disease, and the like. An effort is made to avoid confusion by referring seldom to different types of lymphoblastoma, although one type may produce certain manifestations more often than another and the percentage of types vary somewhat among cases grouped in various ways. However, the patients all had lesions of a similar pathologic histology and presented many interesting clinical and pathologic features, only a few of which are to be commented upon.

Symptoms due to lymphoblastoma within the abdomen are of every description and depend upon the location and precise character of the lesion. They may arise from enlargement of abdominal lymph nodes, lesions with or without ulceration within the gastrointestinal tract, and from tumor-like growth infiltrating or pressing on organs or tissues, or originating within them. Such abdominal lesions may not produce symptoms referred directly to their sites, but due to pressure on nerves, invasion of bone, compression of vessels, and other structures, cause pain in the legs and back, edema of the lower extremities and other symptoms and signs

external to the abdomen. Gastrointestinal symptoms of a toxemic sort may arise in patients with lymphoblastoma but without abdominal lesions. It is believed that symptoms of this origin and without abdominal disease are seldom, if at all, included in the statistics given concerning early symptoms and hence the discussion essentially concerns those arising from greater or smaller lesions within the abdomen.

Frequency and Character of Early Symptoms Due to Abdominal Lesions. One hundred and nineteen, or 25 per cent of the 477 patients with lymphoblastoma, had as their initial symptom one referable to an abdominal lesion or else such a symptom was the most prominent early one to indicate they were not well. A second group of 71 patients now dead (20 per cent of all) developed symptoms referable to abdominal disease early in the course of their illness, but other sorts of symptoms were definitely initial ones. These figures indicate that lymphoblastoma commonly causes initial and early symptoms due to abdominal lesions and evidence of disease occurred here in the 477 cases with very great frequency in the latter two-thirds of each patient's illness. In an occasional patient, following a few years of freedom after the regression of an external lesion, symptoms appeared which pointed to a recurrence within the abdomen. Swollen external nodes were then often absent. Such patients as well as many others with early or initial abdominal symptoms underwent an abdominal operation with an incorrect preoperative diagnosis often because of improper evaluation of the history, the blood, Roentgen ray findings and the like.

TABLE I.—INITIAL SYMPTOMS REFERABLE TO AN ABDOMINAL LESION THAT OCCURRED IN 119 OF 477 CASES OF LYMPHOBLASTOMA.

Chief presenting symptom.	No. cases.	Associated symptoms referable to an abdominal lesion.	No. cases.
Pain in abdomen	43		27
Pain in back	27		14
Marked gastric symptoms	15		34
Marked intestinal symptoms	7		38
Pain in legs (left, 4; right, 4; both, 1)	9	(left, 10; right, 11; both, 13)	34
Edema of legs (left, 2; right 1)	3	(right, 3; both, 1)	4
Enlarged nodes in groin (as symptom) (left, 5; right, 3; both, 1)	9	(left, 2; right, 6; both, 2)	10
Pain in groin (left, 1; right, 2; both, 1)	4	(left, 7; right, 4; both, 1)	12
Genito-urinary (frequency, nocturia, etc.) (both ♂)	2	(13, ♂; 6, ♀)	19
Jaundice	0		3

In other cases, fever and so forth, was the chief initial symptom when dependent upon disease in the abdomen. With or soon after presenting initial symptom referable to an abdominal lesion there were often symptoms of general ill health, such as abnormal fatigue, asthenia, loss of weight, and so forth.

Table I synopsizes the location and character of symptoms referable to abnormality within the abdomen that occurred in the 119 cases with one or more initial symptoms of this sort. The most prominent one is listed as initial. There occurred in most cases

more than one such symptom and often many. These associated symptoms are listed as such and occurred with or soon after the symptom listed as initial. Late in the course of the disease patients often showed other manifestations of abdominal lesions. These occasionally differed in type from those which were noted early.

Abdominal Pain. Slight discomfort has not been recorded as pain. Abdominal pain was often of great intensity, its character intermittent or continuous, dull or sharp, varying with the position of the lesion. The locus of pain was about as frequent in one part of the abdomen as another except for the left lower quadrant, where pain rarely was present. Pain sometimes occurred suddenly, occasionally much alleviated by position, and every feature associated with abdominal pain occurred among the cases. Its occurrence caused the belief of many physicians and often for a long time, that there was present one of the common nonmalignant diseases. Gall bladder disease was perhaps the one most frequently simulated often because of diseased lymph nodes in the region of the larger bile ducts or lymphoblastoma within the jejunum or lower duodenum.

Pain in Back. Pain in the lower part of the back as an initial symptom was prominent. A diagnosis of various bone lesions that may occur from disease of the vertebra and adjoining bones was frequently made. Back pain was excruciating in 11 of the 27 patients, who experienced it as the initial symptom, while a like intensity was not uncommon late in the disease. It often radiated to the abdomen and at times developed concurrent with abdominal pain. Similarly, abdominal pain occasionally radiated to the back. Pain in the back was apt to be greater on one side than the other. Change of position was frequently followed by relief, but the position varied in the different patients. Relief in some was obtained by assuming a totally different position from that which alleviated another. Sometimes the pain was viselike or cramplike; often of a dull, persistent intensity. It commonly passed down the posterior, and less frequently down the anterior aspects of one or both legs, and had many different varying features. A Roentgen ray study of the spine of 50 cases, nearly all over forty years of age, who had backache at some time during the course of the disease, including 22 that had such pain early, showed in fully 30 per cent the presence of chronic arthritis. None of these 50 cases showed lesions of the vertebræ due to lymphoblastoma, as may occur and cause pain. This discovery often led to the belief that arthritis was the sole cause of the pain. We have observed that arthritis in some part of the body is very common in older patients with lymphoblastoma and repeatedly have detected spinal arthritis in such cases when no backache occurred. It is not necessary that some lesion discovered in the region of a given symptom is its cause. The back pain experienced by these patients was not at least wholly due to spinal

arthritis because in spite of its presence the pains were very often rapidly and markedly alleviated following Roentgen ray or radium irradiations of lymphoblastomatous lesions causing pressure in the abdomen. An example of this type of case has been reported in detail by Isaacs.[3]

Gastrointestinal Symptoms. Each instance of gastrointestinal symptoms recorded in Table I was sufficient to be a definite feature. Relatively mild gastric and intestinal symptoms common in any chronic disease and during the course of lymphoblastoma are excluded. Epigastric distress, especially after meals, was frequent, sometimes quite severe and suggested the diagnosis of peptic ulcer or gall bladder disease. Gastrointestinal symptoms and signs at times simulated those of appendicitis and operation occasionally revealed lymphoblastoma involving the appendix or adjacent parts. Nausea and various symptoms due to increased amounts of gas throughout or within certain parts of the digestive tract were common, sometimes very marked and frequently of paroxysmal nature. Vomiting was relatively rare. Rolling sensations occurred with lymphoblastoma involving the walls of the stomach. "Heart burn" was seldom noted but decrease or absence of free hydrochloric acid in the stomach contents following a test meal was common and the rule in cases with lymphoblastoma of the gastrointestinal tract. In a few instances, gastric symptoms were initial or the most prominent early ones when the most marked lesion appeared to be in the mediastinum.

The intestinal symptoms included pain; diarrhea; constipation, often progressively increasing; distention and soreness referable to the colon, and rarely rectal tenesmus. Attacks of discomfort with a rather sudden onset associated with distention were more common than continuous discomfort. Diarrhea alternated with constipation both when lesions were present within and external to the intestines. Attacks of diarrhea lasting days to weeks occurred at varying intervals of time for many months, while more or less continuous looseness of the bowels was also an early as well as a late manifestation. Marked increasing constipation was the initial symptom for two patients, in both due to pressure of a mass on the colon. This symptom, as a concomitant early one dependent upon various mechanisms, was more usual than diarrhea.

Initial gastrointestinal symptoms often persisted a long time before there was other evidence of lymphoblastoma. Roentgen ray studies, if yielding positive information, were apt to lead to an incorrect pathologic but correct anatomic diagnosis. The roentgenologic aspects of the stomach in this group of cases is to be presented by Holmes, Dresser and Camp, and a further consideration of the Roentgen findings is for consideration at a subsequent date. Often the gastrointestinal history, especially of patients with lymphoblastoma of the intestinal tract, was not a normal one for a long

time, often many years, before symptoms have been attributed to lymphoblastoma.

Intestinal or gastric perforations occurred in 2 per cent of the 401 dead cases. In 2 cases symptoms due to perforation of the gastrointestinal tract, one of the stomach, the other of the small intestine, were the first due to lymphoblastoma to be at all significant. Perforation of the stomach resulting from lymphoblastoma lesions occurred in 2, and of the intestine in 3 other cases long after the onset of disease. Severe hemorrhages from the gastrointestinal canal never occurred early, but did do so in 1 per cent of all the cases. Much fat in the stools not due to the exclusion of bile was rare but was observed dependent upon obstruction of the lacteals due to extensive disease of the lymphoid tissue of the intestines and adjacent lymph nodes.

Jaundice. Jaundice may be produced from compression of the larger biliary ducts and from infiltrations of the liver by lymphoblastoma lesions. In this series jaundice was not recorded as an initial symptom, but it was the first symptom of a case of Hodgkin's disease seen recently, and Pepper[4] reports a somewhat similar instance. Of the 401 dead cases, 23, or 6 per cent, are known to have developed definite jaundice. If all cases had been observed continually it is believed more would be recorded as showing this symptom. It is also thought, because of our own observations, that the lesser grades of clinical jaundice and jaundice of the plasma during the course of lymphoblastoma are to be observed in more than 10 per cent of cases. Jaundice in these patients often fluctuates in degree and may disappear spontaneously as well as after irradiation treatment to return often after a longer or shorter time.

Enlargement *per se* of the liver and spleen seldom caused symptoms. If so they were due to pressure or the increased weight of the organs causing a dragging sensation. Perisplenitis causing pain, did occur rarely. Enlargement of one or both of these organs was rather common but seldom occurred early. The spleen became palpable, sometimes only shortly before death. The absence of an enlargement of the spleen should not lead to diagnostic error.

Glycosuria (Pancreatic Involvement). Lymphoblastoma may invade the pancreas and in 1 case may have arisen within it. In this case glycosuria was noted early and later became marked. In 3 of the 401 deceased patients glycosuria, associated with the invasion of the pancreas with lymphblastoma, developed late in the disease, being slight in 2 and marked in 1. Glucose in the urine was demonstrated constantly in 4 other cases, in whom probably it was not related to lymphoblastoma of the pancreas. Thus 2 per cent of all 401 cases are recorded as showing definite glycosuria.

Pain in Legs. Pains in the legs occurred with great frequency among the 477 patients, often appearing late in the disease. Even

so, as an initial symptom it occurred in about 8 per cent and as an early symptom in 28 per cent of the 119 cases in which the chief initial one was referable to an abdominal lesion. These pains were referred more often to the posterior than the anterior aspect of the legs. They were of various types and were associated with pressure on different nerves within the abdomen. Although one leg was most commonly more painful than the other, both were equally involved in some patients. The pain was sometimes dull and generalized, but frequently followed the course of one or more nerves, being mild or intense, stationary or darting, constant or intermittent. It was occasionally confined to the upper third of the leg, but more apt to extend to the foot. The patients usually suffered the most when standing, but some had the greatest pain when lying down. Stooping and motion relieved a few, but rest gave relief to the majority. Pains in the legs were apt to be associated with backache, but often occurred independent of pain in the abdomen or back. In some cases there was a long interval between backache, abdominal pain, or both, and pains in the legs. When pains in the legs were the initial symptoms, abdominal or back pain usually developed later in the disease. Rarely, there was an interval as long as five years. Areas of numbness were associated occasionally with pain in the legs. Marked involvement of the spinal cord by invasion or compression with lymphoblastoma sufficient to cause practically complete paralysis below the waist occurred as a late manifestation in 16 (4 per cent) of the 401 deceased cases. In many, pains in the legs had been one of the early symptoms. Such cases, of course, showed changes in the reflexes, but an absence of their alteration was noted in most cases with pains in the legs even after they had been prominent a long time.

Edema of Legs. Edema of one or both legs occasionally appeared as a symptom and usually long after many others. It occurred rarely as an initial symptom. In a number of instances pain disappeared as edema began. The edema could be attributed to the obstruction of the blood and lymphatic flow by pressure of masses of lymphoblastoma and distinctly enlarged lymph nodes usually were present in the groin or in the lower part of the abdomen when edema developed. However, in those cases where edema occurred early these external nodes seldom were detected as enlarged, and it was then often difficult to palpate any definite abnormal masses within the lower abdomen. However, sooner or later it was possible to locate the masses.

Genitourinary Symptoms. Genitourinary symptoms were recorded in 65 (16 per cent) of the 401 deceased cases. They occurred much more often late in the patient's illness than early, and more often in men than women. Nocturia, definitely beyond any degree experienced before the onset of lymphoblastoma and frequency of urination often were noted, while dysuria and hematuria were not

common. Such symptoms were rare as initial ones but those of prostatic obstruction were the first in one case and frequency of urination in another, evidently associated with large nodes in the region of the neck of the bladder. The former case had a lymphoblastoma, apparently arising in the prostate, like cases described by Quinby[5] and Fukase.[6] These genitourinary symptoms may arise not only from hyperplasia of the lymphoid tissue in the prostate and pressure by masses on the lower genitourinary tract, but quite possibly from hypertrophy of the submucosal lymphoid structures in the genitourinary tract. In true Hodgkin's disease, however, Symmers[1] has noted these rarely to be involved. Hematuria can be dependent on invasion of the kidney. Incontinence developed in those cases with marked involvement of the spinal cord.

Menstrual Disorders and Pregnancy. Menstrual disorders are common in most chronic diseases and in lymphoblastoma need not be attributed to disease within the abdomen. Cessation of menstruation as well as decreased amount or irregularity of flow rarely occurred early but rather often as a relatively late symptom, influenced in some, no doubt, by irradiation therapy. A rare case developed an increased menstrual flow.

Pregnancy causes symptoms referable to the abdomen and it is thus of some interest to note that of the 51 married women with lymphoblastoma, between the ages of twenty and forty-five years, eleven, or 21.5 per cent, bore children after the onset of their disease. One of these women gave birth to 2 children three years apart. All of the 13 children appeared healthy although 2 died at birth from obstetrical accident.

Enlarged Nodes and Pain in Groin. The chances are exceedingly great that when nodes become enlarged in the groin due to lymphoblastoma they are secondary to disease within the abdomen. As a symptom, their enlargement in the groin was the initial one rarely, and seldom was noted by the patient in association with his early symptoms. The condition of these nodes as noted by the physician is mentioned *below*. Pain in the groin occurred both as an initial and early symptom and was referable to pressure by nodes often situated so as not to be detected by the patient. Several such patients had been told their trouble was due to a hernia. Both enlargement of nodes in the groin and pain in this region may be present over a year before other symptoms appear.

Pigmentation (Suprarenal Capsule Involvement). Another symptom that may occur with abdominal lymphoblastoma is pigmentation of the skin, probably often dependent upon impairment of the suprarenal capsules. Undoubted abnormal pigmentation of the skin resembling that seen in Addison's disease developed in 19, or 5 per cent, of the 401 patients and it was not to be attributed to the administration of arsenic. The mucosa of the mouth was involved less often than the skin of the face, backs of the hands, axillary,

genital region and trunk. A low blood pressure is the rule in lymphoblastoma, and in these 19 patients the systolic pressure was usually not above 100 mg. of Hg. Nearly all showed evidence of extensive disease within the abdomen and some were proved to have the suprarenal tissue partially destroyed by invasion. Pigmentation was not noted until rather late in the course of the disease except in 2 patients, in 1 of whom it appeared soon after the initial symptoms, which were pronounced epigastric distress, abnormal fatigue and weakness.

Early General Symptoms and Skin Lesions. General symptoms of ill health as abnormal fatigue, night sweats, anorexia, loss of weight and the like were frequently noted with, or soon after the initial symptom referable to abdominal disease appeared, in the 119 patients of this group. Upon critical inquiry this type of symptom could at times be dated as arising earlier in the history of the disease than the one considered initial by the patient and referable to the abdomen. Fever coincident with early abdominal symptoms occurred, but was not the rule. In some of the 401 cases paroxysms of fever and associated symptoms were initial ones. Chills and fever occurred at the onset in 3 cases with definite symptoms directly referable to the abdomen. In other cases chills and fever developed early but there was no distinct disorder clearly referable to abdominal lesions. However, the fever in some of these patients at a later date was considered due to abdominal lymphoblastoma. Thus, as has been noted by Longcope and McAlpin[7] and others, chills and fever may be initial symptoms of such cases. In fact fever is more frequent and the patient's temperature higher with internal lymphoblastoma than with other types and usually such cases are the ones to give the Pel-Ebstein temperature curve.

Itching and various skin lesions are well recognized as manifestations of lymphoblastoma. Eighteen (15 + per cent) of the 119 patients with initial symptoms referable to an abdominal lesion suffered markedly with pruritus for a considerable period of time during the earliest part of their disease. Ten of these patients also developed distinct skin lesions due to lymphoblastoma. Dermatological symptoms are important to note as they help lead to a correct diagnosis. Among all the 477 cases studied some had apparently a disorder of the skin as their initial symptom of lymphoblastoma, and like fever it may have been the first manifestation due to disease arising within the abdomen.

Physical Signs. In conjunction with the different symptoms referable to an abdominal lesion many kinds of physical signs were present; for example, spasm and tenderness of various parts of the abdomen and back, albuminuria, alterations in the blood, the presence of palpable masses and so forth. Abdominal masses were detected in 42 (35 per cent) of the 119 patients with initial symptoms referable to lymphoblastoma of the abdomen when they first

reached the clinic. In some cases the presence of abdominal masses was doubtful, and when such was the case they were found if operation was done. This was often weeks and even over a year after the appearance of the original symptoms. Ascites developed late but was not of common occurrence. The fluid was rarely chylous or chyliform. Dilated abdominal veins, sometimes very marked were observed late in the disease and in 1 case an extensive collateral venous circulation was obvious four years before death.

Enlargement of External Nodes. Lymphoblastoma remained confined to the abdomen in but 11 per cent of the 119 patients with initial symptoms referable to abdominal lesions. Some of these died as the result of a surgical operation and thus before the disease had run its natural course. The detection of definite enlargement of lymph nodes in the groin was of distinct assistance in establishing the diagnosis. The frequency in these patients of abnormal nodes in the groin at different times during the course of their disease is shown in Table II. The enlargement was often slight and yet beyond a degree that reasonably could be due to a trivial cause. Although in 27 per cent of the cases these nodes were enlarged early, it was surprising to find how often physicians had attributed no significance to them. In a greater number (58 per cent), the inguinal nodes became enlarged late. This is to be expected because they almost always become diseased subsequent and not prior to the appearance of lymphoblastoma within the abdomen. These nodes averaged larger late than early in the course of the disease, when usually those of both sides of the groin were involved, in contrast to one side, which was the rule when the patients first reached the clinic.

TABLE II.—CONCERNING EXTERNAL LYMPH NODES OF 119 CASES WITH INITIAL SYMPTOMS REFERABLE TO AN ABDOMINAL LESION (25 PER CENT OF 477 CASES OF LYMPHOBLASTOMA).

Lymph Nodes in Groin.		
In association with early symptoms.	Number of cases.	Per cent. of cases.
Enlarged, often but slightly; usually on one side	32	27
Not abnormal	76	64
Unknown	11	9
Later in disease.		
Enlarged, usually both sides	69	58
Not abnormal	30	25
Unknown	20	17
Other Lymph Nodes.		
Enlarged external nodes, other than in groin associated with early symptoms (neck, one side, 17; both sides, 1; axilla, 3; neck and axilla, 5)	26	23
No evidence (about 60 per cent by examination, 40 per cent by history) of enlargement of these nodes in association with early symptoms	93	77

The occurrence of enlarged external nodes in other parts of the body than the groins and in association with the early symptoms was recorded in 23 per cent of the 119 cases. Oftentimes the number of nodes abnormally enlarged was few and their size not great. Spontaneous fluctuations in their appearance caused their significance to be underrated. Their occurrence is a distinct help for diagnosis. Examination of the mediastinum for enlarged lymph nodes in cases presenting abdominal and back symptoms that are not explained readily occasionally will aid to establish the diagnosis of lymphoblastoma. The Roentgen ray studies of the thorax made early in a few such cases often revealed enlargement of mediastinal tissue. It happened a number of times that enlarged nodes above the clavicle, particularly the left, were the first or only external ones to appear in cases with lymphoblastoma originating in the abdomen. When this took place nodes in the groin usually did not become enlarged. Enlargement of external nodes seldom developed to a marked degree in these 119 cases, so that the lesions remained confined, especially to the abdomen and thorax.

However, data at hand suggest that if abnormal-sized nodes are searched for they will be found in cases with lymphoblastoma, particularly involving internal structures more often than is suggested by the figures given, which are partly compiled from records made by others than ourselves.

Further reference to symptoms and signs will not be given, but a consideration of the ages of the patients and the length of their illness will be discussed.

Age and Sex Incidence. The age incidence of the patients with initial and early symptoms referable to an abdominal lesion is shown by two curves in Fig. 1. The one for those having early, but not such initial, symptoms is rather similar to that for all 477 cases of lymphoblastoma.[2] The curve for those whose initial symptoms were of the sort discussed indicates their greater frequency in the later than earlier years of life.

Lymphosarcoma and pseudoleukemia are forms of lymphoblastoma apparently most frequent at the ages of thirty-five to forty-five years and prone to involve the gastrointestinal tract. Cases of this sort were particularly common among those with initial symptoms referable to lesions below the diaphragm. Hodgkin's disease was over twice as frequent (40 per cent) among those with early, but not initial, abdominal manifestations than in the group with original symptoms of this kind. This condition is one of youth. Thus, the pathologic type of case explained the difference in the age incidence of the two groups of patients. However, why the one group had these sorts of symptoms as initial ones and the other did not, but experienced them early, is not entirely clear. One reason is that Hodgkin's disease rarely causes large or multiple primary lesions of the gastrointestinal tract, while lymphosarcoma

and pseudoleukemia relatively often do so—lesions which can cause symptoms before the disease spreads. The Hodgkin's patients with early abdominal manifestations very probably may have had their diseases arise here, but its dissemination permitted a symptom not referable to the abdomen before the lesions therein were of sufficient size to cause symptoms. The early abdominal manifestations in this group might also be considered as indicative of a rapid advancement of the disease to the abdomen from other parts. Such is suggested by the fact that the duration of their illnesses after initial symptoms was more frequently shorter than that of those with the initial symptoms, but who were usually older (Fig. 2). This is not necessarily true, for the duration of all sorts of lymphoblastoma in younger males, who are especially prone to have the Hodgkin's type, averages shorter than in older males with various types of lymphoblastoma.[2]

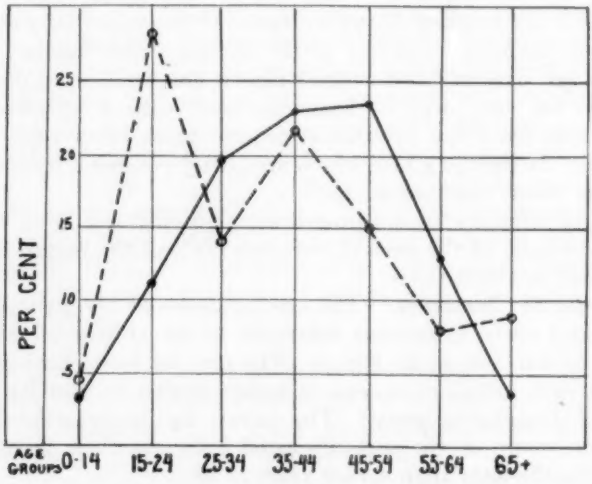

FIG. 1.—Age distribution of 104 cases of lymphoblastoma with initial (●——●) and 71 cases with early (o- - - -o) symptoms referable to abdominal lesions.

Among the cases with initial symptoms referred to below the diaphragm the ratio of males and females was essentially the same as for all 477 cases, namely, about 2 to 1. There was a slightly greater frequency of males among those with early, but not initial, symptoms referable to an abdominal lesion.

Duration of Disease and Treatment. Lymph-node enlargements and other lesions due to lymphoblastoma may exist in the abdomen many months, if not perhaps years, without giving rise to symptoms or signs illustrating the adaptability of the abdominal viscera to withstand a gradually increasing pressure. Just when in the course of disease symptoms arise will depend somewhat on the location of

the lesion. This makes it most difficult to estimate the duration of disease, the onset of which can only be dated from the first symptom or sign referable to it. Large masses can develop in the abdomen without apparently impairing health or being in the least bothersome. When finally lymphoblastoma tumors do so, the first symptom is then long after the lesion originated. It is, thus, not illogical to expect the duration of such patients' illness, dated from the first symptom, to be shorter than for those whose symptoms or signs arise from disease in other parts of the body, where the lesion is more apparent to the individual himself. The data indicate this to be so.

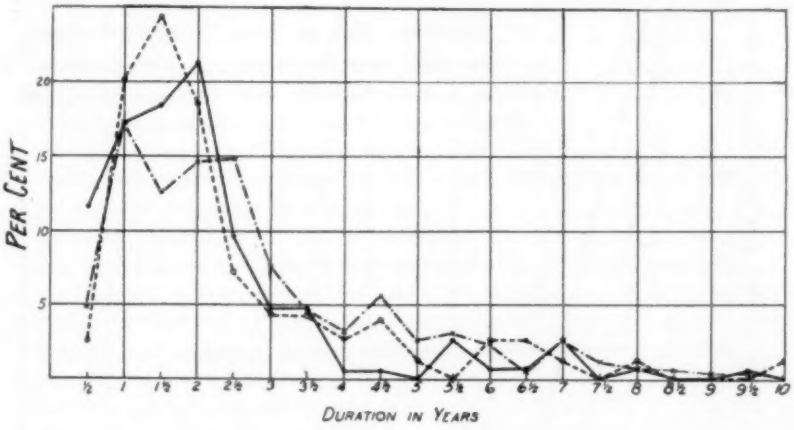

FIG. 2.—Duration of 400 cases of lymphoblastoma grouped according to the occurrence or absence of early symptoms referable to an abdominal lesion. Initial symptoms (104 cases) referable to an abdominal lesion (•——•). Early but not initial symptoms (69 cases) referable to an abdominal lesion (o- - - -o). Such symptoms (227 cases) not present early (x·-·-·-x).

Figures 2 and 3 give information concerning the duration of lymphoblastoma and indicate the probabilities of the length of life after the development of symptoms referable to abdominal lesions. The chances are greater for a short than a relatively long life after abdominal lymphoblastoma causes pain and other symptoms, than when such symptoms have not appeared. Sixteen (3 alive) or 13 per cent of the 119 patients whose initial symptoms were referable to abdominal lesions have had their disease over four years. In two it was of the Dorothy Reed type. Ten, or 8 per cent, have had lymphoblastoma for over six years. All except 3 of the 16 patients were over thirty-five years of age. Enlarged nodes in the groin were recorded as the initial symptom for 5 of these patients. In 3 the nodes were dissected out, and 1 of them, alive six years after operation, shows no definite signs of disease. About two years

after removal of the groin nodes in another case, a lymphoblastoma mass was removed from a portion of the small intestine by resection. This patient died five years later with multiple signs of the disease. It is probably that the reason the duration of these 5 cases is recorded as long is because the external nodes appeared early, permitting the

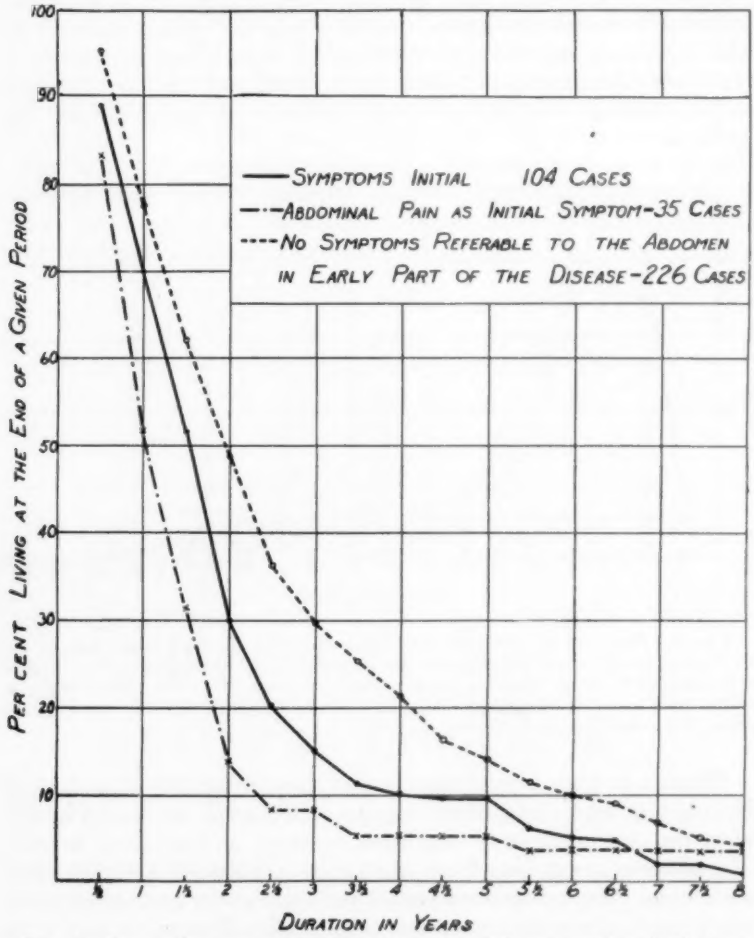

FIG. 3.—Summation curves showing duration of 365 cases of lymphoblastoma grouped according to the occurrence or absence of early symptoms referable to an abdominal lesion.

onset of disease to be dated sooner after its actual beginning than usually appears possible in abdominal lymphoblastoma. In 4 of the 16 patients abdominal pain was the initial symptom. In 2 this was due to a lymphoblastoma of the small intestine; the tumors of both were removed by surgery. A lymphoblastoma was con-

fined to the rectum in another, who remains alive ten years after treatment by surgery and radium. The fourth patient had several palpable abdominal masses when pain first occurred in this region, and now, six years after an exploratory operation and continued irradiation, he remains in fair health. Darting pain in the legs in 1, and backache in 2, were the initial symptoms of 3 others, while the first symptoms of the remaining 4 were of a dyspeptic sort, 1 having recurring diarrhea as a feature.

Some of these 16 patients were markedly alleviated by irradiation treatment.* The same was true for many other cases among the total 53 deceased patients that were irradiated and who had initial symptoms referable to the abdominal lesions. However, the data analyzed in different ways show no essential difference for the frequency of the length of duration after the onset of symptoms of the 53 cases irradiated and the 48 that were not. The figures are slightly in favor of the irradiated cases. Abdominal operations, most of which were exploratory, and but few of a therapeutic nature, were performed on about 30 per cent of these 119 cases. All sorts of preoperative diagnoses were made, but lymphoblastoma rarely. The diagnostic aspects of this group will not be discussed here. In spite of the fact that surgery seldom could be of a therapeutic sort, when such is possible it probably offers life extension to the patients. This is illustrated especially by the 2 cases that had excision of a portion of the small intestine containing lymphoblastoma and the case with a rectal lymphoblastoma referred to above. Such cases are not known to have lived so long after symptoms when any other form of treatment was employed.

It seems probable that often suitable irradiation treatment has not been directed to the abdomen of patients with lymphoblastoma. Many of our patients received their first treatment with Roentgen ray or radium when abdominal disease was advanced or extensive. Undoubtedly the abdomen becomes involved long before important symptoms occur, due to lesions within this part of the body. Slight symptoms referable to the abdomen, back, or legs in cases of lymphoblastoma, should always arouse suspicion of disease in the abdomen and be met by appropriate treatment. Perhaps it is wise to consider in some cases irradiation treatment to the abdomen before there appears any prominent symptom referable to disease here, as practised by Soiland.[8]

Concerning Early Diagnosis. Cases of lymphoblastoma with the first important symptom referable to an abdominal lesion will probably be diagnosed earlier and more often if the condition be recalled when patients present symptoms of a lack of sense of well

* It is a pleasure to acknowledge that many of the irradiation treatments were given by Dr. George W. Holmes and his associates. Their work is appreciated greatly, as is that of numerous members of the staff of the Huntington Hospital, who administered treatment.

being and have symptoms and show signs, even of a minor grade, of the types that have been discussed. We believe that cases of this sort have often had sufficient signs to establish a diagnosis of lymphoblastoma long before it was actually made. A thorough clinical investigation, including proper study of blood, should be made of any patient, and such work, combined with an imagination for the possibilities of disorders present, is what will lead to the more frequent early diagnosis of all forms of lymphoblastoma.

Summary. Twenty-five per cent of 477 patients (401 dead, 76 living) with lymphoblastoma, exclusive of lymphatic leukemia, had as their initial symptom one referable to an abdominal lesion. Twenty per cent of the deceased without such initial symptoms had symptoms referable to abdominal disease early in the course of their illness. Late in the disease such symptoms occurred with very great frequency.

Symptoms due to lymphoblastoma within the abdomen are protean and may simulate many kinds of disorders. They often lead to an incorrect diagnosis, but need not necessarily do so if the condition be recalled and all facts evaluated properly.

Abdominal and back pain, often intense; pains in the legs and various gastrointestinal symptoms may be prominent early ones. Genitourinary symptoms, jaundice, signs of invasion of the pancreas, adrenals, and spinal cord are apt to appear late. Fever and skin manifestations may occur early and even be initial when the chief lesion is in the abdomen. Pregnancy may run its normal course in patients with lymphoblastoma, and is not unusual.

In but 27 per cent of the 119 cases with initial symptoms referable to abdominal lesions, was there enlargement of lymph nodes in the groins early, and at this time only 23 per cent had enlargement of other external nodes.

Cases of this sort occur more often in the later than the earlier years of life; even so, cases with early, but not initial, symptoms referable to abdominal lymphoblastoma occur particularly in the third decade of life.

After the appearance of symptoms referable to an abdominal lesion, the prognosis for a long duration of life is worse than when such manifestations are absent.

Irradiation of abdominal lesions can alleviate markedly these patient's symptoms. It has not prolonged definitely, on the average, the duration of disease but probably occasionally can do so. Likewise, rarely the duration of a case may be extended by a radical surgical operation.

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FAMILIAL PERNICIOUS ANEMIA.

A Discussion of an Unusual Group of Cases with a Consideration of Achlorhydria as the Dominant Etiologic Factor.

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The recent observation of a patient with pernicious anemia, five other members of whose family had died of it or had had the same disease, suggested an investigation of the other members of the family group, which disclosed the fact that four more had either marked hypochlorhydria or complete achlorhydria. This finding, in turn, suggested an examination of the literature on pernicious anemia, especially that of the last two decades, with particular reference to this feature.

Because of the varied methods of dealing with the problem this mass of literature seems, at first, to lack any thread of continuity, but we hope to be able to show that such a thread, though broken in places, is present. Probably the most interesting work on pernicious anemia of the last fifteen years has been that on the familial occurrence of pernicious anemia, following the investigations of Schauman[1] and Meulengracht.[2] Indeed the one fact in the accumulated data which stands out with striking clearness is the apparent indication that in pernicious anemia there may be an important hereditary factor. No comprehensive review of the literature will be given in this preliminary report, the primary purpose of which is the presentation of a group of cases which offer striking confirmation of this conception.

Twenty-five years ago pernicious anemia was almost universally considered to be entirely a "blood disease." This conception apparently resulted from a tendency to accept the opinions of the German, Biermer,[3] rather than the fundamental work of Addison, and also from the prominence which at just that period was given

to cytologic studies. Under the term "pernicious anemia" Biermer grouped "a number of different forms of anemia which have certain characteristic features in common, a spontaneous origin without clear etiology."

During the last twenty-five years, however, through the efforts of many workers, among whom the names of Hunter,[4] Ewald,[5] Zadek,[6] Woltman,[7] Schauman and Hurst[8] mark successive mile stones, a conception of the disease has developed which is far more complete and hopeful than that which obtained in 1900. From the conception that pernicious anemia is strictly a blood disease we have come to feel that the blood changes do not constitute the entire picture but that they bear much the same relation to the disease as does the blood picture to the entire syndrome of lead poisoning. In both of these diseases a low-grade persistent toxemia is now considered to be the essential causative factor. It may be well, therefore, to review very briefly the contributions made by the men cited.

In 1890, Hunter, whose large series of studies extend over many years, suggested for the first time that pernicious anemia is the result of a *persistent but insidious toxemia* and that it is essentially due to the absorption of poisons from the alimentary tract.

The absence of free hydrochloric acid in pernicious anemia was first noted by Cahn and von Mering[9] in 1886. Ewald and Zadek have proved conclusively that there is an intimate relationship between achlorhydria and pernicious anemia, the former finding achlorhydria in each of 75 cases, and the latter in each of 50 cases. The most recent extensive work in this direction has been that of Levine and Ladd[10] who found that achlorhydria was present in all but 1 of 105 cases of pernicious anemia. In 1913 Faber[11] overthrew the generally accepted view that the achlorhydria is secondary to the anemia and proved definitely that the achlorhydria is *primary and not a result of the anemia.* Since 1913 numerous investigators have substantiated Faber's findings.

The association of anemia with subacute combined degeneration of the spinal cord was noted as early as 1887 by Lichtheim[12] who reported 3 cases of anemia with symptoms referable to the spinal cord. Since that time such symptoms have been recognized with increasing frequency until in 1918 Woltman published a paper in which he gave conclusive evidence of spinal-cord changes in 80.6 per cent of 150 cases. Our own experience at the Cleveland Clinic fully corroborates this figure. As in the case of the achlorhydria, the spinal-cord changes were at first thought to be secondary to the anemia, but soon the proper relationship was established and it became apparent that *both the anemia and the cord degeneration are the result of some obscure chronic intoxication* and may appear independently. Hurst very aptly sums up this point of view in the following sentences: "No definite line can be drawn between pernicious anemia accompanied by spinal-cord changes and subacute

combined degeneration of the spinal cord accompanied by anemia. The difference is simply one of degree and depends upon whether a hemolysin or a neurotoxin is the more active."

The literature regarding *the familial occurrence of Addison's anemia, and its relation to constitutional achylia gastrica* with which this paper is primarily concerned may be briefly summarized as follows: Twenty years ago the occurrence of Addison's anemia in several members of the same family was considered a rarity, but we now know that it happens with considerable frequency. Less than fifteen years ago Cabot[13] made the following statement in a review of a series of 1200 cases: "The writer twice found the disease in the same family, two sisters being attacked in one instance and a brother and sister in another." Since this was written many cases of multiple occurrence in a single family group have been reported and undoubtedly this condition will be found with increasing frequency wherever it is carefully sought.

In 1891 Klein[14] reported the occurrence of 3 cases of pernicious anemia in a single family—in two sons and a daughter of parents who had not had anemia. In 1899 Bramwell[15] reported the incidence of the disease in a father and two sons and in 1900 Caccini[16] reported the occurrence of anemia in a mother, a son and a daughter. Cabot's report of 2 cases which has already been mentioned, follows the above in chronological sequence. In 1910, Gilbert[17] reported the occurrence of Addison's anemia in two sons of one family. In 1911, Patek[18] described a family group in which two brothers and one sister, an uncle and a cousin died of the disease. In 1912, Gulland[19] reported an unusual group in which five members of one family, a father, three children and an uncle, all died of the disease; and in the same year Willson[20] described 5 cases in a single family. In 1914, Roth[21] and Bartlett[22] presented cases of pernicious anemia, the first including the occurrence of the disease in two sons in one family; the second, its occurrence in a father and in three sons all of whom died of the disease. In 1920 Meulengracht reported a very interesting group in which four brothers and a cousin had pernicious anemia; and during the past four years a large number of additional reports have appeared in the literature, Faber,[23] Levine and Ladd, Schauman, Mustelin,[24] and Gilford[25] having reported cases of particular interest. These references are surely sufficient to sustain the statement that familial Addison's anemia occurs with considerable frequency. An exhaustive review of the recent literature would include many more cases but it is unnecessary to add them to those already cited. We may, however, add here that of 11 carefully investigated cases which have been seen within the last six months at the Cleveland Clinic, a family history of the multiple occurrence of the disease was found in 4. The history which forms the basis of this paper I believe to be the most unusual family history on record.

The important steps in the development of conceptions regarding

the nature of pernicious anemia which have thus far been reviewed may be briefly summarized as follows: (1) The early conception of Hunter that the disease results from the absorption of poison from the gastrointestinal tract; (2) the interrelationship of anemia and combined lateral sclerosis; (3) the practically universal occurrence of achlorhydria gastrica in both of these conditions and the fact that this achlorhydria precedes the development of each. It is at this point that Hurst offers a theory, the most acceptable working hypothesis of the cause of Addison's anemia which has so far been presented. Its essential features may be restated as follows: The fundamental predisposing cause of pernicious anemia is achlorhydria. In most cases the disease is caused by the constitutional and congenital absence of gastric juice, but it may be caused by acquired achlorhydria. This condition removes the normal bactericidal function exerted by the acid of the gastric secretions, permitting the development in the upper portion of the small intestines of a bacterial flora which gives rise to neurotoxins and hemolytic poisons.

For a complete presentation of Hurst's[8] conception, the reader is referred to his various papers which have been collected into a single volume. Hurst's investigations open many problems which are still unsolved, such as the exact nature of the bacterial growth, and the development of pernicious anemia in the presence of the artificial achlorhydria which follows massive resection of the stomach for ulcer, several cases of which have been reported; but these are definite, clear cut problems and we may reasonably hope that they will be solved. In an attempt to solve the second of these problems, Vanderhoof[8a] has attempted to produce experimental anemia after the resection of the stomach in dogs, but has not yet reported his conclusions. Our own bacterial studies based upon clinical cases, which promise valuable information, will be reported in a later paper.

It is not surprising that the familial occurrence of pernicious anemia should have interested investigators, since it offers a promising point of attack on the entire problem. Many theories have been advanced to explain this phenomenon, among which the achlorhydria theory is certainly the most logical. Achlorhydria is transmitted from one generation to another and thus predominates in members of a family group. If it can be shown that achlorhydria is a predominating characteristic in families, one or more members of which have pernicious anemia, then there would seem to be no question but that "congenital achylia gastrica is undoubtedly the hereditary factor in cases of familial Addison's anemia." Weinberg,[26] Martins,[27] and Faber all report cases of anemia in which constitutional achlorhydria is a marked family characteristic; and the writer feels certain that gastric analysis would reveal similar conditions in the members of the immediate family of any patient suffering with pernicious anemia.

Since I became interested in this problem I have demonstrated

this relationship several times, the most remarkable group of cases being that which suggested this paper.

Case Reports. On August 21, 1924, a woman, aged forty-four years, presented herself at the Cleveland Clinic for a general physical examination. The case proved to be one of well-advanced pernicious anemia with predominant cord changes. Upon taking the family history, we learned that her mother, a sister and a brother had all died of the same disease. Another brother was ill at the time, and she had been on her way to visit him, suspecting that he might have pernicious anemia, but totally unaware that she herself was a victim of the disease. When we investigated the brother's case, we learned that her suspicion was well founded, for he had the same disease. Here we had a remarkable group of cases, consisting of five members of a single immediate family who have either died from the disease, or were in its late stages.

In 3 of these cases we have been fortunate enough to obtain direct and conclusive evidence which has substantiated the diagnosis. In the case of the mother and of one daughter it was too late to obtain direct evidence, but the histories and indirect evidence are so conclusive that there can be little doubt as to the accuracy of the diagnosis.

It was possible for us to examine six other members of this family group for the signs of Addison's anemia, and especially for alteration in the gastric secretions. In each case the fractional gastric analysis was made. A graphic description of the results of the investigation of this group is given in the accompanying chart and the individual cases are reported in detail.

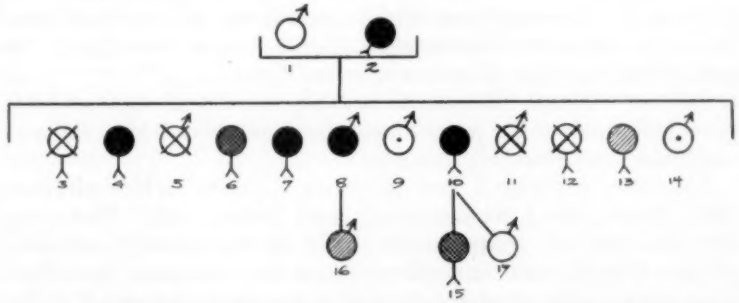

FIG. 1.—Family Group of Cases of Pernicious Anemia. No. 1—Father; no definite history, did not have anemia. No. 2—Mother; died of pernicious anemia (Case No. II). No. 3—Died in infancy. No. 4—Daughter; died of pernicious anemia (Case No. V). No. 5—Died in infancy. No. 6—Daughter; achlorhydria (Case No. VI). No. 7—Daughter; died of pernicious anemia (Case No. III). No. 8—Son; died of pernicious anemia (Case No. IV). No. 9—Son; living and well, normal gastric secretion, normal blood (Case No. VIII). No. 10—Daughter; died of pernicious anemia (Case No. I). No. 11—Son; killed in accident at thirty-six, no data. No. 12—Daughter; died in labor at twenty-seven, no data. No. 13—Daughter; achlorhydria (Case No. VII). No. 14—Son; we have never been able to get in touch with this member of the family. No. 15—Granddaughter, daughter of No. 10; achlorhydria (Case No. IX). No. 16—Grandson, son of No. 8; achlorhydria (Case No. X). No. 17—Grandson, son of No. 10; normal secretion and blood.

CASE I.—The initial case report is that of the woman whose history initiated the study of this group. This patient was a well-nourished, well-developed woman, aged forty-four years. Her chief complaint was of general weakness and some difficulty in handling her feet in walking; she complained also of a feeling of numbness in both legs and to a lesser degree in the fingers. She had lost about 10 pounds in weight during the six months preceding her examination, but still weighed 180 pounds and except for a slight pallor, appeared to be in very good health. She complained of considerable pain and discomfort at the menstrual periods. Her temperature at the time of examination was 100, pulse 110, and blood pressure 150 systolic, 80 diastolic. Physical examination revealed a fibroid tumor of the uterus about the size of a large orange, which undoubtedly was responsible for her distress at menstrual periods.

The neurologic examination gave the following significant findings: *Sensory:* Poor differentiation between heat and cold over the lower extremities, this impairment being most marked over the left ankle and leg where heat was persistently mistaken for cold; inaccurate tactile sense, the sense of light touch being gone over both legs, although there was fairly accurate differentiation between pressure by the head and by the point of a pin; vibratory sensation completely lost on both sides below the knees and impaired from the pelvis to the knees.

Neuromotor. Normal reaction of the pupils and no impairment of the external muscles of the eyes; no impairment of speech nor tremor of the tongue. Definite ataxia disclosed when patient attempted to carry out the finer movements of coördination with the fingers. Knee-heel test fairly accurate but sense of position of the lower extremities inaccurate. Marked ataxia in walking—the gait resembling that of advanced tabes dorsalis.

Reflexes.—Biceps, triceps and radial present both right and left; knee jerks and ankle jerks absent both right and left; Babinski suggestive and Romberg positive.

Laboratory Findings. Red cell count, 2,750,000; white cell count, 5600; hemoglobin, 80 per cent; color index, 1.35. The smear showed a marked variation in the size of the red cells with numerous oversized deeply staining erythrocytes, and an occasional myeloblast. Fractional gastric analysis showed a complete absence of hydrochloric acid in the stomach secretions. The urine was entirely normal. A spinal puncture showed the fluid to be under normal pressure, cells and globulin not increased; the Wassermann test and gold curve negative. The blood Wasserman test was also negative.

This evidence indicated definitely the following diagnosis: (1) Subacute combined degeneration of the spinal cord; (2) pernicious anemia; (3) uterine fibroid. The patient remained in Cleveland for several months and was treated under the direction of the Clinic.

The following medication was prescribed: Dilute hydrochloric acid, 2 to 4 cc. well diluted in water, four times daily; Fowler's solution in graded doses; and Blaud's mass, grains v, three times daily.

The red-cell count responded very promptly, rising to 4,300,000, but the spinal-cord symptoms were not affected. The patient left Cleveland in the late fall of 1924, and we received word in January, 1925, that the blood count was again falling. In February, 1925, she contracted pneumonia, and died after three days' illness.

CASE II.—This woman for whose history we must rely upon her daughter, was the mother of Case I and was the first of this family group to develop pernicious anemia. She died thirty-five years ago at the age of forty-six years, the cause of death as recorded in her death certificate being pernicious anemia. The oldest living daughter, who was twenty years old at the time of her mother's death, states that her mother had had "stomach trouble" for a number of years, but this never seemed serious and otherwise she enjoyed good health. Two years before her death she began to complain of exhaustion and although she appeared to be well and did not lose in weight, she was unable to carry on her household duties. She took a rest cure which seemed to help her considerably, but soon after returning home she began to decline very rapidly, became short of breath, her skin took on a yellow color and the family were told she had pernicious anemia and would not get well. During the last few months of her life she complained bitterly of a "dead sensation" in her limbs, and rapidly developed an ataxia which culminated in a loss of ambulatory power. The physician who cared for this patient has died, and it is, therefore, impossible to secure laboratory data if, indeed, any ever existed. The history of the case, however, is so definite both as to the course of the anemia and the development of the signs of changes in the cord that one can hardly question the diagnosis.

CASE III.—Daughter of Case II and sister of Case I. In August, 1919, this member of the family first sought medical attention because of soreness of the tongue and pain in the feet, legs and fingers. She had enjoyed good health previous to that time except for rather frequent intestinal upsets characterized chiefly by diarrhea. She also gave a history of having been troubled a great deal with a sore tongue, the glossitis having appeared at intervals during several years previous to her first medical examination. In 1919, the patient consulted Dr. Charles F. Hoover at Lakeside Hospital. He has kindly furnished data from his examination, which may be summed up briefly as follows: The patient was a well-developed and apparently well-nourished individual of middle

adult life. The skin had a somewhat waxy appearance. The essential positive findings from the physical examination were the glazed, reddened tongue, which is characteristic of achlorhydria, and signs of early spinal-cord degeneration. In addition to the disturbance in sensation noted above there was also a definite ataxia both of fingers and of the lower limbs with diminished vibratory sense.

The significant laboratory findings were as follows: Red blood cells, 2,450,000; hemoglobin, 65 per cent; white cell count, 3850. Study of the stained smear showed a marked variation in the size of the red cells with many large, deeply staining erythrocytes and a few normoblasts. A fractional gastric analysis extending over a period of two hours showed complete absence of hydrochloric acid. Dr. Hoover's diagnosis at this time was that of primary anemia. The patient was seen again at Lakeside Hospital in May, 1920. At that time her red count had increased to 2,370,000 and the hemoglobin was 80 per cent. She still had a highly marked disturbance of sensation in both the upper and the lower extremities. A fractional gastric analysis at this date gave the same findings as the previous one.

A year after her second visit to Lakeside Hospital the patient evidently experienced one of the characteristic remissions of this disease; her color improved, the blood count increased and she seemed to be much better; but a relapse followed within nine months and she went to New York to be under treatment at Bellevue Hospital. There the diagnosis of pernicious anemia was confirmed and she was given blood transfusions in an effort to improve her condition as she was rapidly failing. In all she received seven transfusions but there was no evidence of any sustained response to this treatment. She rapidly grew weaker and died in March, 1921.

Case IV.—The son of Case II and brother of Cases I and III. The diagnosis of pernicious anemia was made in 1922 by a physician who had not known of the family tendency toward the disease until I wrote to him for information regarding this patient. The diagnosis was made clinically before any laboratory work was done, and the history is the usual one of this disease without evidence, in this case, of spinal-cord changes. Between 1922 and 1924 the patient had several remissions during which he seemed "almost well," but from April, 1924, there were no further remissions, the patient being confined to his bed until his death on October 11, 1924. A blood examination made in the laboratory of a reliable hospital on April 23, 1924, gave the following findings: Red blood cells, 1,570,000; white blood cells, 9200; hemoglobin (Fleischl), 45 per cent, color index, 1.4. The stained smear showed marked variation in the size of the cells with many large deeply stained red corpuscles.

The hematological diagnosis was "a well-marked case of pernicious anemia."

CASE V.—Eldest daughter of Case II and sister of Case I. She died thirteen years ago at the age of forty-seven years. This patient was the first of this generation in the family to develop the disease, a diagnosis of pernicious anemia having been made more than two years prior to her death. When I attempted to obtain a reliable medical statement about this case, I learned that the physician who cared for her and had made the diagnosis died during service in the World War; but I believe the story told by a sister who was with the patient during her illness offers sufficient evidence. I shall give the history as nearly as possible as it was told to me: "Sister had been ill for some months before calling a physician, she tired very easily and complained of a sore tongue but was otherwise the picture of health. Finally the local physician was called who made little of her trouble at first and advised rest. However, she failed to improve, began to complain of pain in her feet and legs and then her skin took on the same queer yellow color mother's had when she was ill. A consultant was called in who made a very careful examination, including blood tests, and told us she had pernicious anemia. She did not improve under treatment. The pain in her legs became more severe and she had great difficulty in walking and later in using her hands. In spite of her prolonged illness, she did not lose in weight until the last few months. Toward the end she failed very rapidly, and died after prolonged suffering." The death certificate gave pernicious anemia as the cause of death.

The following reports concern members of the family who at the present time are apparently in excellent health. The findings in these cases are of even more interest than those which have preceded, in that they afford a very striking argument in favor of the hypothesis we are investigating—namely, the causative rôle achlorhydria may play in pernicious anemia and especially in the familial form of the disease.

CASE VI.—Daughter of Case II and sister of Case I. Aged fifty-two years; apparently in normal health; physical examination revealed no abnormal condition. Blood picture entirely normal; no complaint except a frequent sensation of epigastric heaviness. Fractional gastric analysis showed a complete achlorhydria.

Time.	Free HCl.	Total HCl.
15 minutes	0	0
30 minutes	0	4
45 minutes	0	8
60 minutes	0	4
120 minutes	0	0

CASE VII.—Daughter of Case II and sister of Case I. Aged thirty-eight years; no complaint; health excellent; blood picture

normal. Fractional gastric analysis showed a marked hypochlorhydria.

Time.	Free HCl.	Total HCl.
15 minutes	0	0
30 minutes	0	0
45 minutes	0	11
60 minutes	13	18
90 minutes	8	12

CASE VIII.—Son of Case II and brother of Case I. Aged forty years; health excellent; no complaint; normal blood picture. Fractional gastric analysis gave a normal secretory curve.

CASE IX.—Grandchild of Case II and daughter of Case I. Aged nineteen years; general health excellent; no complaint except of rather frequent attacks of indigestion, especially after eating heavy foods. Tongue presented appearance usually described in textbooks as associated with achlorhydria. Physical examination revealed no abnormal condition; blood picture normal. Fractional gastric analysis showed a complete achlorhydria.

Time.	Free HCl.	Total HCl.
15 minutes	0	0
30 minutes	0	0
45 minutes	0	4
60 minutes	0	6
90 minutes	0	8
120 minutes	0	3

CASE X.—Grandchild of Case I and son of Case VIII. Aged thirty-one years; general health good; always nervous; no other complaint. Physical examination revealed no abnormal condition; blood picture entirely normal. Fractional gastric analysis showed a marked hypochlorhydria.

Time.	Free HCl.	Total HCl.
15 minutes	0	0
30 minutes	0	3
45 minutes	0	4
60 minutes	0	4
90 minutes	12	14
120 minutes	5	20

This case showed no free HCL at the end of an hour and with the usual one-hour test would have been diagnosed as one of achlorhydria.

CASE XI.—Grandson of Case II and son of Case I. Aged twenty-one years; no complaint. Physical examination showed nothing which concerns us in this discussion. The blood picture was normal and the gastric analysis showed a normal secretion.

Discussion. From the work of the various investigators in this field whose conclusions have been briefly summarized in the earlier

part of this paper, and on the basis of our own experience especially in the unusual family group here reported, we conceive that the achlorhydria of Addison's anemia is the factor essential for the development of the disease and that it is often congenital. When the normal gastric secretions are absent, their germicidal function is consequently lacking, and there follows the development of a low-grade bacterial flora in the upper gastrointestinal tract. The toxins elaborated by these organisms over a sufficient period of time are the direct cause of the changes which we recognize clinically as pernicious anemia.

We wish to emphasize that the development of this theory is not due to the work of any one investigator, but to each of various workers who have approached the problem from widely different directions. To Hunter, however, belongs the credit for the fundamental conception and to Hurst the credit for correlating with Hunter's idea the additional data which have accumulated in the last two decades.

Though we believe that achlorhydria is usually congenital, nevertheless it is conceivable that it may be acquired. Thus achlorhydria may follow massive resection of the stomach such as is now frequently performed. It is conceivable in view of this theory that some years later the patient might develop Addison's anemia, and, in fact, we know that this does happen.[8] Similarly dogs whose stomachs have been removed may develop a blood picture which is typical of anemia, though up to now this evidence remains suggestive rather than conclusive.

In the unusual family group here reported a mother and four children have died of the disease and among six other members of the family whom we have had the opportunity to examine, only two had a normal gastric secretion; two had a complete achlorhydria and two had a very marked hypochlorhydria, closely approaching an achlorhydria. None of these later cases, which ranged in age from nineteen to fifty-four years, showed an abnormal blood picture. We know that those members of the family who died of the disease had an achlorhydria, therefore in a group of eleven individuals in one family we find that nine had lack of acid in the gastric secretions and five of these developed pernicious anemia.

The argument may be advanced that about 3.5 per cent of people have achlorhydria, and this figure is far above the incidence of primary anemia. There are two answers to such an argument: The first is that the writer is certain that the disease occurs with far greater frequency than either general medical opinion or vital statistics would lead one to believe; and the second is that such an argument in no manner weakens the contention that the achlorhydria is the primary predisposing factor in pernicious anemia. It would be just as logical to exclude diseased tonsils as a cause of

nephritis simply because thousands of people with diseased tonsils fail to show evidence of kidney disease.

We feel so strongly that achlorhydria gastrica is a sign of grave clinical importance that we consider that every patient presenting this condition should be regarded as a potential case of Addison's anemia, and that the administration of hydrochloric acid should be started immediately, even though there are no gastric symptoms. We feel also that all members of a family in which Addison's anemia has been found should be thoroughly examined and should have a gastric analysis made, in order that the administration of large doses of the acid may be started at once in those who have hypochlorhydria or achlorhydria.

With regard to the administration of acid, either in cases of fully developed anemia or in potential cases, we are fully in accord with the conclusions of Shaw,[28] who has shown that the usual 10-minim doses are useless and we therefore give from ½ to 1 dram of dilute hydrochloric acid, well diluted with water, four times daily. As smaller doses than these fail to bring the acid content of the stomach to a figure which approaches the minimum normal acidity they can have very little, if any, physiologic effect. It is usually advisable to start with smaller doses and gradually increase the amount, as otherwise diarrhea may be produced. If the acid is objectionable to the patient it may be given in well-sweetened lemonade or in cider. The dilution of the acid should be in the proportion of not less than 1 dram of the dilute—10 per cent—acid to 500 cc. of water or other medium. This is divided into smaller amounts, part being taken before the meal, part with the meal and part afterward. I am giving these details concerning the administration of the acid because the patient must take it for the rest of his life, and it is of the utmost importance to have his coöperation, which will surely be lost if he is dismissed merely with the direction to take a teaspoonful of acid in a glass of water.

Can the development of pernicious anemia be prevented by the administration of hydrochloric acid in the manner described to patients who have an achlorhydria and a familial history of the disease? Is similar therapy of value in the early stages of the disease? These questions cannot be answered until our clinical cases have been followed for the next five or ten years, or without an exhaustive experimental investigation. Such an experimental investigation is at present under way. We are approaching the problem from two directions: (1) We are carefully studying the intestinal flora of clinical cases and its relation to bacterial foci in the mouth and throat; (2) we are attempting to produce the disease experimentally in animals in which we can vary our controls more definitely. Though we have reason to believe that the anticipated results will be secured, years of careful study will be necessary before any definite conclusions can be drawn.

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THE ETIOLOGY OF HEART DISEASE.

A Clinical Study of 623 Cases with Certain Observations on Race and Climate.

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A preliminary study[1] seemed to indicate that climate and race might be factors of interest in a clinical investigation of the causes

of heart disease. Therefore, we have arranged two carefully studied series of cases, the patients of one group residing in or near the state of Virginia and the patients of the other group coming mainly from Massachusetts or neighboring states. All cases were suffering from or presented signs of organic heart disease; no case with a functional cardiac disorder alone has been included in either series.

The etiologic classification used here is based entirely on that suggested by White and Myers.[2, 3] The definition of each type of heart disease need not be repeated as many medical centers now use this or a similar classification of cardiac diagnosis. The name of each diagnostic group will call to mind the type of heart disease in question.

As already indicated, two series of cases are presented for comparison. Series I includes 300 cases of organic heart disease admitted to the medical service of the University of Virginia Hospital from October 1, 1923 to January 1, 1926. Seventy of these were private room cases. Each patient was investigated by history, physical examination and the usual laboratory methods, and each one was seen personally and examined by one or more of us. In addition to this, electrocardiograms were made on 192 patients of this series, 71 received Roentgen ray studies, and 21 of the 59 dying under observation came to postmortem examination. Carefully recorded percussion measurements have been found valuable and accurate, judging from the Roentgen rayed cases and those coming to autopsy. Fossier[4] has even remarked on certain advantages of percussion over radiology in determining heart size. The few autopsies obtained, while of little value statistically, were of great help in stimulating better clinical observation. In no case in which we failed to obtain an electrocardiogram was the etiology of the heart condition seriously in doubt, although galvanometer tracings are highly desirable in every heart case. A well taken history and a careful and accurate physical examination are the two most important procedures in determining the etiology of heart disease.

Series II* comprises 323 cases of organic heart disease admitted to the medical service of the Massachusetts General Hospital from March 19, 1924 to November 1, 1924. This series has been studied in a similar fashion and is entirely comparable to Series I, except that no private-room cases occur in it. In both Series I and Series II, diagnostic problems were often discussed by various members of the medical visiting staff of each hospital and their judgment has been helpful in many instances, and is frequently reflected here.

* Series II was obtained by one of us in conjunction with others, while going over a large number of cases to be shortly published as an etiologic study of heart disease in New England.

TABLE I.—GENERAL ANALYSIS OF 623 CASES OF ORGANIC HEART DISEASE.

Series I and II.	Sex and race.						Age groups.														Auricular fibrillation.				Heart block.																			
	I.[1,2]				II.[3]																				A-V.																			
	White.		Negro.		White.		0 to 10.		10 to 20.		20 to 30.		30 to 40.		40 to 50.		50 to 60.		60 to 70.		70 +.		Permanent.		Paroxysmal.		Auricular flutter.		Digitalis.		Organic.		Intraventricular.		Pulsus alternans.		Paroxysmal tachycardia.		Congestive failure.		Angina pectoris.		Coronary occlusion.		Pericarditis.	
	M.	F.	M.	F.	M.	F.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.
Rheumatic	25	21	7	5	56	63	3	10	17	38	18	17	8	26	7	17	3	9	2	2			8	14	2	3	1	3	1	4	5	7	1	1				5	16		1				4	9
Rheumatic + Hypertension	1		1		1	1							1	1		1	1																											
Rheumatic + Arteriosclerotic	2																		1		1		1								1						1								
Rheumatic + Bacterial endocarditis	2	2			3	1				2	1	1	2	1	1																						1							
Rheumatic + Effort syndrome						1																																						
Rheumatic + syphilitic					2							1				2																1												
Rheumatic + Hypertensive + syphilitic						1										1																												
Arteriosclerotic	33	10	7	4	25	16									8	4	15	11	20	21	11	5	16	3	4	1		2	2		3	3	5	5					18		15	10	3	3		
Arteriosclerotic + Hypertensive	28	20	21	12	36	29							3		8	15	27	22	28	22	15	6	15	5	1				2		1	4	4	9	2	2	1		39		6	8	3		3[4]	
Angina pectoris						2														2																								
Hypertensive	6	14	9	15	16	23					4	2	9	5	16	10	13	15	2	6		1		3									1					18			1			4[4]	
Hypertensive + Emphysema						1										1																												
Emphysema	1														1																													
Syphilitic	1	1	9	4	13	1					4	1	5	3	1	4	4	5	1	1									1										1					
Syphilitic + Hypertensive	2		3	1	2	1							1		2	1	2	2	1										1		1		2						5		3	5				
Syphilitic + aneurysm	5		7		2								1		1	1	5	1	4		1																		3						
Thyroid	1	3		2	2	8						3	1	5	3	2	2								2	1				2									3		3				
Thyroid + Hypertensive	1	2		2	3	5				1		2	1	1	1	1	3	2	1																	1		1						
Bacterial endocarditis					2											2																												
Congenital	2	1			4	1	1		1	3		1	1	1																													
Unknown	3	1	1	2	1	1	1						2	1	1	1	2		1				1	1		1													1						
																																							1						

[1] Ratio of white to negro hospital admissions 3.3 to 1 for the period of this study. [2] Virginia. [3] Massachusetts. [4] Uremic.

Table I records sex, race, age groups, certain arrhythmias and other features for the diagnostic groups of each series. Table II gives the percentage incidence of the diagnostic or etiologic groups in Series I and II. Table III indicates the incidence and type of valvular affections by etiologic groups for the entire study. Space does not permit a repetition of all the facts contained in these tables. Certain features of interest, however, deserve comment.

TABLE II.—INCIDENCE OF ETIOLOGIC GROUPS IN 623 CASES OF ORGANIC HEART DISEASE.

Etiological groups.	Series I.		Series II.	
	No. cases.	Per cent.	No. cases.	Per cent.
Rheumatic	58	19.33	119	36.80
Rheumatic + hypertensive	2	0.66	2	0.61
Rheumatic + arteriosclerotic	2	0.66		
Rheumatic + bacterial endocarditis	4	1.33	4	1.23
Rheumatic + effort syndrome			1	0.30
Rheumatic + syphilitic			2	0.61
Rheumatic + hypertensive − syphilitic			1	0.30
Rheumatic + all complications	66	21.98	129	39.85
Arteriosclerotic	54	18.00	41	12.66
Arteriosclerotic + hypertensive	81	27.00	65	20.12
Arteriosclerotic + Rheumatic	2	0.66		
Arteriosclerotic + all complications	137	45.66	106	32.78
Hypertensive	44	14.66	39	12.07
Hypertensive + arteriosclerotic	81	27.00	65	20.12
Hypertensive + rheumatic	2	0.66	2	0.61
Hypertensive + syphilitic	6	2.00	3	0.92
Hypertensive + thyroid	5	1.66	8	2.47
Hypertensive + emphysema			1	0.30
Hypertensive + rheumatic − syphilitic			1	0.30
Hypertensive + all complications	138	45.98	119	36.79
Syphilitic	15	5.00	14	4.33
Syphilitic + aneurysm	12	4.00	2	0.61
Syphilitic + hypertensive	6	2.00	3	0.92
Syphilitic + rheumatic			2	0.61
Syphilitic + rheumatic − hypertensive			1	0.30
Syphilitic + all complications	33	11.00	22	6.77
Thyroid	6	2.00	10	3.16
Thyroid + hypertensive	5	1.66	8	2.47
Thyroid + complications	11	3.66	18	5.63
Angina pectoris			2	0.61
Angina pectoris + other diagnoses	28	9.33	26	8.04
Emphysema			1	0.33
Bacterial endocarditis			2	0.61
Congenital	3	1.00	5	1.54
Unknown	7	2.33	2	0.61

TABLE III.—VALVE LESIONS IN 623 CASES OF ORGANIC HEART DISEASE.

Etiology.	Number of cases.		Aortic regurgitation.		Aortic regurgitation + stenosis.		Mitral regurgitation.		Mitral stenosis.		Mitral regurgitation + mitral stenosis.		Aortic regurgitation + mitral regurgitation.		Aortic regurgitation + mitral stenosis.		Aortic regurgitation + stenosis + mitral regurgitation.		Aortic regurgitation + stenosis + mitral stenosis.		Aortic regurgitation + stenosis + mit. regurgitation + mit. sten.		Aortic stenosis + mitral regurgitation + mitral stenosis.		Aortic regurgitation + mitral regurgitation + mitral stenosis.		Patent ductus arteriosus.		Pulmonary stenosis.		Pulmonary stenosis + interventricular septal defect.		Interventricular septal defect.	
Series	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.
Rheumatic	56	116	6	7	1	1	8	6	15	22	12	36		4	7	7	1			1		9		3	6	20								
Rheumatic + hypertensive	2	2	1					1	1																	1								
Rheumatic + bacterial endocarditis	4	4					1	2			2		1	2																				
Rheumatic + syphilitic		2								1						1																		
Rheumatic + effort syndrome		1														1																		
Rheumatic + arteriosclerotic	1		1																															
Arteriosclerotic	3	3	1	1			2	2																										
Arteriosclerotic + hypertensive	9	4	5	2			4	2																										
Hypertensive		1						1																										
Hypertensive + syphilitic	3	2	3	2																														
Syphilitic	10	11	10	11																														
Syphilitic + aneurysm	8	1	8	1																														
Congenital	3	5																																
Bacterial endocarditis		2												1												1	1	2		3	1		1	
Totals	99	154	35	24	1	1	15	14	16	23	14	36	1	7	7	9	1			1		9		3	6	22	1	2		3	1		1	

Heart Disease in the Negro. Heart disease is decidedly more common in the negro than in the white. Observing the ratio of admission to the hospital given in the footnote Table I Series I it appears that heart disease is almost twice as frequent in the negro as in the white. This is slightly higher than the figures obtained from a study of vital statistics. The definitely higher incidence of heart disease in the negro is shown, however, by this also.

The death rate per 100,000 from heart disease in Virginia for 1921[5] was 172.6 for negroes and 122.5 for whites. The death rate per 100,000 from heart disease in the same state for 1924[6] was 202.6 for negroes and 142.4 for whites. In Massachusetts the death rate per 100,000 from heart disease was 185.2 in 1921, and 200.6 in 1924. There are no figures available for negroes and whites separately. In Virginia, the negro forms, of course, a much greater percentage of the population than in Massachusetts. Giving death rates per 100,000 from organic diseases of the heart from the Industrial Department of the Metropolitan Life Insurance Company, for the years 1911–1920, Dublin[7] finds the following: white male 118.1, white female 132.3, negro male 189.1, negro female 200.4. He further states, "The greater prevalence of heart disease among colored people is notorious. Colored males show rates from heart disease during the main period of life from 65 to 80 per cent higher than for white males at the same ages; those for colored women are twice as high as for white women at a number of age periods." In a recent article, the same writer[8] gives death rates per 100,000 from heart disease from the same source for 1923 as follows: white male, 113.6; white female, 122.1; colored male, 190.8; colored female, 217.4. Again he emphasizes the increased death rate from heart disease in the negro and particularly the female negro. We have attempted below to explain this in part.

It is interesting to note which types of heart disease are outstandingly more common among the negroes. Hypertensive and syphilitic heart disease are in the main responsible for the increased incidence of heart disease in this race. In Series I, 60 of the 112 negroes or 53.5 per cent had some form of hypertension, excluding also those with syphilitic heart disease. The males and females of this number were almost equally divided. There were 72 of 188 whites or 38.1 per cent having some form of hypertensive heart disease, likewise excluding the syphilitic groups. Twenty-four of 112 negroes or 21.4 per cent had some form of luetic heart disease whereas 9 of 188 whites or 4.7 per cent (6.5 per cent in Series II) were affected with the same malady. Males preponderate distinctly in the colored syphilitic heart disease groups. It appears, therefore, that hypertension and syphilis account for about 75 per cent of heart disease in the negroes and about 45 per cent of heart disease in the whites in Virginia. The higher incidence of heart disease in the negro

female especially at certain ages noted by Dublin has not been explained. It is our impression that a larger series will show that hypertension is probably the factor sought.

Cardiosclerosis alone represents about 10 per cent of heart disease in negroes as compared to about 23 per cent in whites. Peripheral arteriosclerosis is extremely common in the negro and it appears in a great many colored patients in whom signs and symptoms of heart disease are not present. It happened in this study that in many of the cases where arteriosclerosis was considered to be an etiologic factor in the production of the heart condition hypertension was also present. The infrequency of angina pectoris in the negro is discussed below.

Again in Series I, 11.6 per cent of heart disease in the negro is rheumatic in origin, while all forms of rheumatic heart disease in the whites total 28 per cent. Rheumatic heart disease seems to us to be less common among the colored people than the white people of Virginia. Apparently no other direct observations have been recorded on this subject. Both Osler and Weir Mitchell[9] noted the rarity of chorea in the colored race. Admission ratios for acute rheumatic fever per 1000 white and negro army regulars quoted by Faulkner and White[10] averaged almost exactly the same for the ten years 1913 to 1922 inclusive. Vital statistics from the Registration States for 1922[11] show a death rate from acute rheumatic fever slightly higher among the negroes than whites. Whether these statistics are correct or whether the heart is less frequently involved in the negro with rheumatic infection, we are unable to say. The question of the incidence of rheumatic infection in the negro is obviously in doubt and needs a more careful study than that offered by the data from vital statistics.

Rheumatic Heart Disease and Climate. Rheumatic heart disease of all types is almost twice as common in Massachusetts as in Virginia according to this study. All forms of rheumatic heart disease comprise 22 per cent of the 300 cases of Series I; while all forms of rheumatic heart disease in Series II make up 39.8 per cent of the 323 patients. For the four years, June 1921 to June 1925, all chorea and rheumatic fever cases represented 0.7 per cent of the total medical admissions to the University of Virginia Hospital. At the Peter Bent Brigham Hospital for the years 1918–1922[10] a similar ratio was 1.3 per cent. It is interesting, therefore, to note how very closely the ratio of rheumatic infection to rheumatic heart disease in Virginia approaches the ratio of rheumatic infection to rheumatic heart disease in Boston.

Others place the incidence of rheumatic heart disease higher in Boston. Cabot[12] found a 46 per cent rheumatic etiology in 600 clinical cases of heart disease; Hamilton and Hallisey[13] give 58 per cent rheumatic groups in their 356 clinical cases.

Studies by Faulkner and White[10] and Harrison and Levine[14] of the geographical distribution of rheumatic fever show a gradual increase in the occurrence of this disease from south to north in the eastern part of the United States. Our study would tend to show that rheumatic heart disease runs roughly parallel to this. At least the ratio for Virginia and Massachusetts holds true as indicated above.

Angina Pectoris (Paroxysmal Heart Pain). Only instances of angina pectoris or paroxysmal heart pain appear in this study. For the sake of clarity and greater accuracy fatigue heart pain and nervous heart pain have been left out of the discussion. Angina pectoris is apparently decidedly less common in the negro than in the white, notwithstanding the higher incidence of syphilis, arteriosclerosis and hypertension in the former race. In Series I, 6 negroes or 5.3 per cent of the negro heart cases gave a history of paroxysmal heart pain as against 22 whites or 10.2 per cent of the white cases. Apparently the literature does not contain a discussion of this subject. However, mortality statistics[11] from the Registration States for 1922 show the death rate per 100,000 from angina pectoris to be 10.5 per cent in the whites and 3.9 per cent in the negroes. While all mortality statistics leave much to be desired in accuracy, nevertheless the difference here is striking. A subsequent paper by one of us will discuss this subject at greater length. Three of the 6 negro cases with angina pectoris also had syphilitic heart disease, while only 4 of the white cases of Series I fell in this group. The large majority of all paroxysmal heart pain cases in both series were associated with some form of cardiosclerosis. Two cases occurred in Series II with paroxysmal heart pain and no other evidence of heart disease.

Chronic Valvular Heart Disease. Little need be said about this subject which has already been voluminously discussed. In the total study (Table III) of 623 patients 245 or 39.3 per cent were affected with valvular heart disease exclusive of congenital defects and relative mitral regurgitation alone, which was ruled out here as far as possible. This is a decidedly lower percentage of valvular heart disease than the incidence usually recorded in textbooks. Other statistical studies have shown chronic valvular heart disease to vary from 60 per cent to 80 per cent of organic cardiac disorders.

The cause of pure aortic regurgitation has always been of interest and is etiologically accounted for in our 59 cases as follows: Syphilitic, 59.3 per cent; rheumatic, 25.4 per cent; arteriosclerotic, 15.3 per cent. The high percentage of arteriosclerotic aortic regurgitation is at once striking. Others have not found this. Adlmühler[15] found 2.2 per cent of aortic regurgitation due to arteriosclerosis; Hubert[15] 5.5 per cent; Gerhardt,[16] 10 per cent; Romberg,[16] 5.5 per cent. Others in this country have generally believed it to be rarer than

this. In a series of uncomplicated aortic regurgitation cases (24), unselected except that careful Roentgen ray studies had been made on them, recently reported by Lædbetter, Holmes, and White,[17] 13 (or 54.2 per cent) were syphilitic, 6 (or 25 per cent) were arteriosclerotic (and hypertensive) and 5 (or 20.8 per cent) were rheumatic in origin. These findings are corroborative of those reported above. We have excluded syphilis as far as possible in our arteriosclerotic cases. The Wassermann reaction was negative in every case, in 2 arteriosclerotic aortic regurgitation was verified at autopsy, 3 were well over seventy years of age with advanced arteriosclerosis, and the remaining 4 also had Roentgen ray studies supporting the diagnosis.

The fact that rheumatism does not seem to play a large part in the production of aortic regurgitation is misleading here, for rheumatic aortic disease is so frequently combined with mitral disease. Viewing it in this light in pure and combined lesions, rheumatism accounts for 64.5 per cent of aortic disease as recorded in Table III.

Tables I and III still contain a miscellany of undiscussed facts which fall largely outside the purpose of this paper. They have been recorded for completeness and as evidence for the correct choice of the diagnostic groups. Some are worthy of a passing comment. Series I gives cardiosclerosis as the main associated finding in auricular fibrillation, which Series II indicates to be rheumatic heart disease. This is to be expected as the former and the latter preponderate respectively in Series I and II. The incidence of pulsus alternans is too low as alternation of the pulse following premature beats would not be discovered except with routine arteriograms on the hypertension cases. In Series I a record of congestive heart failure has been included which shows that about one-third of the patients of this series entered the hospital with this form of failure.

Further reports from various locations will be necessary to determine the major cause of heart disease for the entire United States. In spite of the high incidence of rheumatic heart disease in certain areas, it is probable that for all ages hypertension is the most potent single etiologic factor in the production of heart disease for the entire country. Fahr[18] believes this to be generally true and estimates that 50,000 people in the United States die from this cause yearly.

We wish to emphasize the importance of etiologic diagnosis in heart disease as the main step toward outlining a program of prevention. Dublin has aptly said, "Out of systematic study and full records in every case will grow adequate methods of prevention."

Summary and Conclusions. 1. Organic heart disease is almost twice as common in the negro as in the white.

2. Hypertension (53.5 per cent) and syphilis (21.4 per cent) are the chief etiologic factors producing heart disease in the negro.

3. Angina pectoris (paroxysmal heart pain) is less common in the negro (5.3 per cent) than in the white (10.4 per cent), despite the fact that syphilis (21.4 per cent) and arteriosclerosis (39.3 per cent) are such important factors in the former.

4. Rheumatic heart disease is almost twice as common in Massachusetts (39.8 per cent) as in Virginia (22 per cent), and this is the largest etiologic group in the former locality.

5. Hypertension as an etiologic factor is somewhat more prevalent in Virginia (45.98 per cent) than in Massachusetts (36.79 per cent), but comprises a large group in each series.

6. Similar studies to this one are to be desired in all parts of the country, or even better the world, as only through etiologic study will grow adequate methods of prevention.

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ETIOLOGIC FACTORS IN ANGINA PECTORIS.

An Analysis of Eighty-Two Cases in Private Practice.

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Although the immediate cause of the attacks of angina pectoris is still immersed in theory, certain etiologic factors deserve discussion when supported by the careful study of 82 cases observed over a long period of time.

Pathologically, disease of the aorta and coronary arteries must be considered the essential morbid process underlying attacks of angina pectoris. Following aortic changes, coronary involvement is common and coronary closure induces the most severe anginal attacks.

There are certain unmistakable characteristics in the typical picture of angina pectoris, including the intense pain with its radiation, angor animi and avoidance of motion while the pain lasts. The condition described as "angina sine dolore" should be excluded from the angina group and be made part of a coronary or myocardial classification. The term "pseudo angina," it is to be expected, will become obsolete.

From the analysis of any series of cases, it can be seen that electrocardiographic changes are found promptly after an attack of angina pectoris and often precede it. This would indicate early myocardial involvement.

In the following analysis, the etiologic factors are taken up categorically to discuss the relation they bear to angina pectoris.

TABLE I.—AGE OF PATIENT AT TIME OF FIRST ATTACK.

Age at first attack.	No. cases.	Percentage.
31 to 35 inclusive	7	9
36 to 40 "	12	15
41 to 45 "	12	14
46 to 50 "	16	20
51 to 55 "	17	21
56 to 60 "	9	11
61 to 65 "	7	7
66 to 70 "	1	1
71 to 75 "	1	1

Age at First Attack. As seen from Table I, almost 25 per cent of the cases with angina pectoris had their first typical attack, mild or severe, before the age of forty years. It is important to recognize this fact, and not to dismiss as insignificant complaints of pain

referable to the heart in young individuals. The largest number of cases occurred between the ages of forty-six and fifty-five years. Above the age of sixty years, the onset of angina pectoris was infrequent. The reason for this may be that a first attack occurring later in life is more often fatal or nearly so in the first attack, and less likely to leave the patient under observation for a period of time.

After the onset of angina pectoris, the period of life expectancy is greatly reduced. In most reports in the literature, the age of its occurrence is usually higher than given in my series, the analysis having been made not from the incidence of the first attack, but from the age of first observation. Cases have been recorded under fifteen years of age.

Sex. It is well known that males are more likely to develop angina pectoris than females, and in our group the number was 65 males and 17 females. In previous reports in the literature, the proportion of females is even smaller than in the series recorded here. The cause of this difference of sexual susceptibility lies mainly in the greater protection in women of the thoracic aorta from physical strain. On the other hand, all the women in my series did have severe sudden stress in their life as a causative factor.

Tobacco and Alcohol. It is doubtful whether tobacco or even alcohol are primary and very important causes, although I believe they cannot be excluded as contributory factors. The question remains unanswered whether the use of tobacco leads to arterial disease. If it does, it may of course provoke aortic lesions out of which angina pectoris may arise. The existence of a type of angina pectoris apparently following the excessive use of tobacco suggests the possibility of a direct relationship. In our series of male cases, 35 gave a history of excessive tobacco and 30 of none or only moderate tobacco. Only one used excessive alcohol, while 33 took none, and 30 took alcohol in moderate or small amounts.

Occupation. From my experience and careful judgment of cases over years, I am convinced that excessive exertion is probably the greatest contributory factor, second only to infectious, senile and other changes producing atherosclerosis; if not equally significant as a cause. The exact anatomic change produced by excessive exertion is not known. I believe that an anatomic change is indeed produced, perhaps even injury to fibers in the aortic wall from increased aortic distention and increased aortic pressure. In favor of this a cogent argument exists in the occurrence of cases soon after severe exertion and attributable to it.

In this regard, it must be remembered that the classification of occupation of the individual cannot materially help us in finding a relationship between excessive exertion and angina pectoris. I mean to say that individuals engaged in very strenuous occupations, paradoxically, are less liable to that sudden strain and that excessive exertion to which people in only moderate or even sedentary occupa-

tions are. That is so first because their hearts are enabled, by adjustment, to undergo rather severe physical strain. Second, for those not generally engaged in strenuous work, excessive strain upon the heart is more possible, and more likely to produce anatomic effects. Contrary to the opinion generally held, from my experience I should be led to say that laborious occupations and athletic pursuits are determinants not so important in the production of angina pectoris as sudden extreme or excessive strain put upon a heart untrained to accept it.

Rheumatism and other Infections. It would seem that the acute infectious poisons such as those of rheumatism and other infectious diseases deserve recognition as important causes initiating vascular changes in the aorta and coronary artery area in early middle age. (See Table II.) This is evidenced in our table in which 24 out of

TABLE II.—DISEASES ASSOCIATED WITH ANGINA.

	No. cases.
Frequent tonsillitis	24
Rheumatism	20
Sinusitis	1
Influenza	4
Gall bladder disease	2
Bronchial asthma	3
Emphysema	6
Cardiac asthma	2
Diabetes	10
Chronic cystitis	2
Polycythemia	1
Cerebral thrombosis	3
Syphilis	3

the total of 82 cases gave a history of frequent tonsillitis; and in 20 a positive history of acute articular rheumatism was obtained. As a direct cause of angina pectoris, rheumatism has not been sufficiently emphasized.

The importance of syphilis as a cause seems, on the contrary, to have been overstressed. In my series, in only 3 cases was the blood Wassermann test or the history of syphilis positive.

Diabetes alone ranks next in frequency as an etiologic or associated factor. The diabetes itself may be due to arterial changes in the viscera and in that way need not bear a purely causal relationship to the cardiac lesion. It was present in 10 of this series of 82 cases of angina pectoris.

Blood Pressure. It is already recognized that no direct etiologic relation exists between arterial pressure and the production of angina pectoris. It is, therefore, to be reasoned that a primary increase in blood pressure is not the essential etiologic factor in the production of atheroma in the aorta or the coronary arteries. We must rather assume that this vascular area at the base of the heart in certain cases undergoes morbid changes as the result of the same toxin which produces a hypertensive effect upon the rest of the vas-

cular system. In this relation, it is interesting to note how frequently patients with extremely high arterial tension will remain free from chest pain or angina pectoris.

TABLE III.—BLOOD-PRESSURE FINDINGS IN ANGINA PECTORIS

Systolic.	No. cases.	Diastolic.	No. cases.	Pulse pressure.	No. cases.
Below 100 mm. Hg.	2	Below 70 mm. Hg.	7	20–30 mm. Hg.	6
100–119 mm. Hg.	7	70–89 mm. Hg.	31	31–40 mm. Hg.	12
120–139 mm. Hg.	26	90–99 mm. Hg.	18	41–50 mm. Hg.	27
140–159 mm. Hg.	19	100–109 mm. Hg.	14	51–60 mm. Hg.	11
160–179 mm. Hg.	12	110–119 mm. Hg.	8	61–70 mm. Hg.	5
180–199 mm. Hg.	6	120–129 mm. Hg.	3	71–80 mm. Hg.	6
200–219 mm. Hg.	5	130–139 mm. Hg.	0	81–90 mm. Hg.	7
220–239 mm. Hg.	4	140–149 mm. Hg.	0	91–100 mm. Hg.	2
240–259 mm. Hg.	1	150–159 mm. Hg.	0	100–130 mm. Hg.	5
260 up mm. Hg.	0	160 up mm. Hg.	0	190 mm. Hg.	1

As seen from Table III, 35 cases showed a systolic pressure below 140 mm. Hg which must be considered entirely within the normal; 47 had a systolic pressure above 140; the majority of these, however, were below 180. The same relation seems to hold true for the diastolic pressure. In 38 cases of this series, the diastolic pressure was below 90 mm. Hg; and in 44, above 90—the majority below 110 mm. Hg.

Three patients with angina pectoris developed cerebral thrombosis with hemiplegia at some time during observation. It is interesting that all these 3 patients had hypertension and lived for some time following their hemiplegia. One patient died after repeated attacks of coronary and cerebral thrombosis. The other 2 are still living, two and five years respectively, after their first anginal attacks.

Kidney Involvement. Involvement of the kidney as indicated by urinalysis was not present in the majority of cases. Albumin was present in 32 and absent in 50 cases.

Relation to Gall Bladder Disease. In a number of the cases (3 in this group, all female), gall bladder disease was found as a coëxisting clinical condition. The presence of gall bladder disease is, of course, a possibility in cases of angina pectoris and often is a complicating feature in differential diagnosis. Where it cannot be excluded, and where the abdominal or hypochondriac symptoms preëxisted and cannot be made part of the angina pectoris, the diagnosis should be made both of angina pectoris and gall bladder disease. The error most often committed is in cases where the gall bladder disease is neglected and the diagnosis is made of angina pectoris alone. Cases of angina pectoris even with abdominal pain are sufficiently typical for the error in the diagnosis not to be committed.

Summary. The etiologic factors are discussed in 82 cases of angina pectoris. Almost 25 per cent of the cases had their first typical attack before the age of forty years. The sex proportion was 65 males to 17 females. Tobacco and alcohol could not be excluded

as contributory factors. Sudden excessive strain is the most important immediate factor preceding the attack, and its effect is more likely to be injurious in individuals engaged in moderate or sedentary occupations in whom the heart and aorta have not been trained to accept sudden strain adaptably. Acute infectious causes such as rheumatism and infected tonsils appear to be important in initiating vascular changes in the aorta and coronary artery area. In only 3 cases was syphilis a factor. Diabetes was present in 10 cases of angina pectoris. There was no direct etiologic relation between arterial pressure and the attacks. Gall bladder disease coëxisted in 3 cases.

RHEUMATIC FEVER.

An Analytical Study of Three Hundred and Ninety-three Cases of Rheumatic Fever and Eighty-nine Cases of Chorea.

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The importance of chronic cardiac disease as an economic load upon both individuals and the community at large has, of recent years, attracted the growing attention of those whose interests lie in the field of preventive medicine. The appreciation of the limits of the problem and consequently the methods necessary for its study have been, in the past, and still are greatly hampered both by incompleteness of vital statistics and by the laws controlling the reporting of disease. However, during the years of the World War, when great numbers of young men, presumably in the prime of life, were examined for draft into the National Army, a broader and more startling concept of heart disease and its importance to society was obtained. The statistics of the Surgeon General's Office show that 2 per cent of those examined were rejected because of damaged hearts.[1] A more striking fact even than this, because it deals with a younger group of individuals, is found in the New York City Health Department records of examination of school children. Here again the incidence of cardiac disease was found to be close to 2 per cent.[1]

Broadly speaking, the etiologic factors, which are operative in the production of these chronic affections of the cardiovascular system, may be divided into two groups; those resulting from infectious disease and those which are attendant upon the physio-

logic-pathologic process of senility and degeneration in the later years of life. This latter class comprises what is probably the irreducible minimum. Of the infectious diseases, however, rheumatism and syphilis bear the onus of greatest responsibility in the etiology of chronic heart disease. Luetic aortitis occurs in from 15 to 25 per cent, conservatively, of all cases of organic heart disease.[2] The diagnosis of rheumatism in this respect has suffered no striking continuous change in the last twenty-five years, varying between 46 and 64 per cent.[1]

The growth of knowledge of this disease comprises in general two distinct chapters. Prior to the seventeenth century the disease which is now called rheumatism was included with gout and other articular diseases under the comprehensive name of arthritis. It is in a posthumous work of the French physician, Baillou or Ballonius,[3] who died in the year 1616, that we find the distinction between rheumatism and gout for the first time clearly drawn, and the word "rheumatism" employed with its present meaning. This conception appears to have met with little if any acceptance by his contemporaries, and it is only in the writings of Sydenham[4] that we find the essential difference between gout and rheumatism once more clearly stated, and the migratory character of the joint inflammation described for the first time.

While the first chapter of the natural history of this disease is concerned with its recognition and separation from other acute articular diseases, the second is filled with the extension of this knowledge as concerns the variety of its manifestations and the sequelæ which may attend it. In Baillie's work, *Morbid Anatomy*, published in 1797, he mentions rheumatism as a cause of enlargement of the heart, saying: "The causes which produce a morbid growth of the heart are but little known; one of them would seem to be rheumatism attacking this organ."[5] In 1827 Seudamore[6] clearly recognized the occurrence of cardiac involvement and cited examples of endocarditis and pericarditis, concluding that: "There is not, probably, a more dangerous form of disease than a sudden seizure of the heart during the inflammatory state of the system in acute rheumatism." Nine years later Bouillaud[7] demonstrated that these lesions are present in so large a proportion of the acute cases that they must be regarded as being no less essentially parts of the morbid process than the arthritis itself. He states his conviction in the following terms: "Dans le rhumatisme articulaire aigu violent, generalisé, la coincidence d'une endocardite, d'une pericardite ou d'une endopericardite est la regle, la loi, et la non-coincidence l'exception." Since that time the field of our knowledge has been extended greatly. The study of its pathology and the recognition of characteristic lesions have led to an increasingly wider concept of rheumatic infection, until today there must be added to the classical manifestations of acute rheumatic fever and

chorea, a variety of lesser and sometimes apparently trivial conditions, which none the less are not infrequently followed by the gravest of complications.

Although the tendency to repeated attacks, the characteristic variation in the disease as seen in adults and children, and the ever-present danger of severe cardiac damage, are common knowledge, their importance is such that they can scarcely be overemphasized. The literature offers analyses of many groups of cases, yet fails to emphasize the growing conviction that rheumatism is essentially a chronic, often a very slowly progressive disease, having periods of activity and latency which are strikingly parallel to the clinical course of tuberculosis and syphilis.

The study of rheumatic infection, however, is one fraught with many difficulties because of the protean forms which it assumes. Many of these are not specific. Others, although unaccompanied by typical arthritic involvements, or evidence of cardiac damage, may in some individuals be followed by the development of classic mitral stenosis. Certain others, however, probably few in number, pass on to uncomplicated recovery without any evidence of permanent visceral damage. Garrod,[8] in 1890, said "If it be once granted that an attack of chorea with endocarditis, or an eruption of a cutaneous erythema, may constitute as truly a rheumatic attack as the most severe forms of articular lesions, it is obvious that arthritis must be deposed from the position of the essential rheumatic lesion, and must be looked upon merely as the most constant and conspicuous of the manifestations of the disease." The extension of our knowledge of the structural and functional changes which follow upon rheumatic infection have necessarily led to the inclusion within it of a wide range of clinical conditions, extending from the apparently trivial "growing pains" of childhood, cutaneous eruptions and sore throat on the one hand, to the frank, acute multiple arthritis and chorea on the other. Not infrequently the diagnosis of rheumatism depends upon *post hoc propter hoc* reasoning, based upon the development of a characteristic heart lesion following some of the less acute types which, of themselves, are not typical of the rheumatic infection.

Because of this variability, and the obvious and unavoidable sources of error which would follow the attempt to include the numerous and less characteristic forms of the disease, only those cases with a hospital diagnosis of acute, subacute or chronic rheumatic fever and chorea have been utilized for this study. They are taken from the records of the Presbyterian Hospital, and comprise consecutive admissions over a period of nine years with the exception of scattered cases, excluded because of incompleteness of the history or work-up.

The types of rheumatic fever included, we define as follows:[9] The acute form is characterized by multiple arthritis, fever and leu-

kocytosis, the symptoms typically yielding to salicylates. The subacute form presents similar manifestations, less marked in intensity. The chronic form is typified either by persistent low-grade fever with mild or transient arthritis, or by chronic cardiac disease characterized by persistent fever and leukocytosis, not associated with bacterial endocarditis.

Analysis of Cases. The 393 cases of rheumatic fever that form the basis of this study show an approximately equal distribution between the two sexes, 198 males and 195 females comprising the group. The chorea group, on the other hand, shows a marked predominance of females, 58 as compared with 31 males. A history of chorea antedating the first attack of rheumatic fever was given by 3.3 per cent of the patients, and among the chorea cases 13.4 per cent gave a history of antecedent rheumatism; 186 cases, or 47 per cent of the rheumatic series, had had at least one previous attack of rheumatic fever; 21 cases, or 23 per cent of the choreas, gave a history of previous signs of this condition.

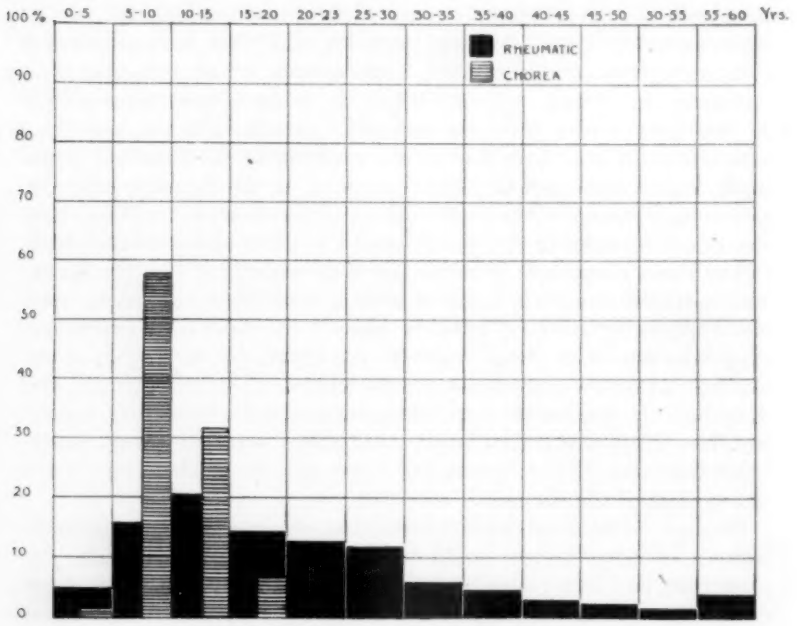


CHART I.—The incidence of first attacks by age groups.

Age of Onset of the First Attack. In 383 of the rheumatic fever series, and in all cases of the chorea group, it was possible to ascertain the age at which the patient suffered the first attack. Those individuals who were first seen in subsequent attacks were able

to date the occurrence of their first acute episode with sufficient accuracy to permit the placing of them in the arbitrary age groups adopted for this study.

It has long been recognized that just as the evidence of this infection differs characteristically in childhood and in adult life, so the liability to rheumatism is far greater in the early than in the later years, although no age is altogether exempt from its attacks. This variation in the incidence of the disease is strikingly illustrated by collecting the cases in five-year age groups. Rheumatic fever shows a smooth regular curve of incidence rising from 4.7 per cent under the age of five years, to a peak of 20.8 per cent between the ages of ten and fifteen years. Thereafter it slowly but progressively falls to 1.5 per cent between the ages of fifty and fifty-five years, with a slight secondary rise in the later years, probably due to confusion with some of the numerous other forms of arthritis. The influence of chorea, however, is seen to be present during a much shorter period. Starting with an initial incidence of 1.1 per cent, its curve rises steeply to a maximum of 58.4 per cent between the ages of five and ten years, falling rapidly then to an incidence rate of 7.8 per cent between the ages of fifteen and twenty years, after which period no initial attacks were found (Chart I and Table I).

TABLE I.—INCIDENCE OF FIRST ATTACKS BY AGE GROUPS.

Age.	Rheumatic fever. (cases.)	Chorea. (cases).
0 to 5	18	1
5 to 10	61	52
10 to 15	80	29
15 to 20	53	7
20 to 25	47	
25 to 30	44	
30 to 35	24	
35 to 40	18	
40 to 45	10	
45 to 50	9	
50 to 55	6	
55 to 60 and over	13	
Total cases	383	89

Incidence of Cardiac Involvement in the First Attack.—The importance of the age factor again becomes apparent in the study of the incidence of heart involvement during the first acute episode of rheumatic infection. Although this analysis is subject to certain errors which could not be excluded, the efficiency of the Follow-up Clinic, where patients are periodically examined following their discharge from the hospital, was of invaluable assistance in this particular phase of the study. Of the rheumatic fever cases 366 were available. These include not only patients seen in the hospital with the first attack, but others seen in later episodes with frank cardiac damage, apparently of long standing, or with normal hearts.

These latter, however, were limited to individuals who gave a definite and precise history as to the age at which they had their first attack and the presence or absence of heart involvement at that time. While data of this sort, obtained from history alone, are open to a considerable degree of inacurracy, yet the error resulting is probably one which tends to reduce, rather than to augment, the gross incidence of heart disease, for many of the early phases of cardiac damage are attended by few, if any, symptoms, and certain others are not always easy of recognition, even on examination of the patient.

A further source of inaccuracy of a somewhat similar nature enters into the findings. A number of cases presenting no evidence of cardiac involvement on physical examination were found to have definitely abnormal electrocardiograms, which warranted their inclusion in the cardiac group. Electrocardiographic examination, however, was not carried out in certain other borderline cases, and these, necessarily, were classified according to the clinical findings while in the hospital and as seen later in the Follow-up Clinic. This error, again, is probably one which tends to minimize rather than to exaggerate the frequency of this incident, for electrocardiographic study was not carried out on many of the earlier cases. Cohn and Swift[10] have pointed out, however, that it is an important and valuable means of determining the earlier and less severe forms of cardiac damage.

Those cases which were classified on the basis of clinical findings alone were considered to have damaged hearts when any of the following conditions were present: definite valvular lesions, enlargement of the heart out of proportion to the degree of fever present, pericarditis, extrasystoles or a persistently rapid pulse. Individuals who gave a history of having had chorea, scarlet fever or diphtheria were excluded.

Of the 366 cases of rheumatic fever, 250, or 68.3 per cent, showed evidence of cardiac disease either at the time of admission to the hospital or during their stay in the wards; 204 of these were subsequently observed in the Follow-up Clinic over varying periods of time, four months being the minimum. In 42 (20.6 per cent) the cardiac condition was definitely improved. On the other hand, 57 cases (27.9 per cent) showed evidence of a progressing lesion and 51.5 per cent were found to be essentially unchanged.

Of 66 cases of chorea similarly analyzed, 34 (51.5 per cent) had definite signs of cardiac involvement upon admission or during their stay in the hospital; 40 of these individuals were subsequently seen in the Follow-up Clinic, and 11 (27.5 per cent) showed improvement in the cardiac condition, while 8 (20 per cent) had progressing lesions; 52 per cent of this group were found to be unchanged.

It is probably unwise to attempt any comparative estimate of the relative frequency or severity of heart involvement in two

groups so unequally matched both as regards number and age of the individuals studied. It would appear, however, that there is little significant variation between these two types of rheumatic infection.

The incidence curve of cardiac involvement in the first attack of rheumatic fever as found in this series approximately follows that of the age at onset of rheumatism. Starting at 38.4 per cent in individuals under five years of age, it rises steeply to 78.1 per cent between five and ten years, and reaches its peak between the ages of ten and fifteen years, when 79.2 per cent are found to have severe forms of cardiac complication in their initial attack of rheumatism. Excluding those cases occurring before the fifth year of life, it is not until the twenty-fifth year is passed that an individual has better than an even chance of escaping cardiac involvement. Although the two age groups thirty to thirty-five and forty-five to fifty years present secondary rises in the incidence rate, this is due in all probability to the relatively small number of cases falling within those limits and not to an actual increase in the frequency of this complication. Similarly, the rise found in the late years of life is probably not the result of rheumatic infection, but rather of confusion in diagnosis due to the association of some of the senile cardiac changes with arthritis. The general trend of the incidence curve seems to support this conclusion, for it is seen that with the exception of the three groups noted, its tendency is steadily downward from the peak of 79 per cent, to 25 per cent in the age group of fifty to fifty-five years (Chart II and Table II).

TABLE II.—THE INCIDENCE OF HEART DISEASE IN THE FIRST ATTACK OF RHEUMATIC FEVER.

Age.	Total cases.	Cardiac involvement.	Incidence rate (per cent).
0 to 5	13	8	38.4
5 to 10	41	32	78.1
10 to 15	58	43	79.2
15 to 20	33	21	63.5
20 to 25	31	19	61.3
25 to 30	36	15	41.7
30 to 35	20	10	50.0
35 to 40	16	5	31.2
40 to 45	11	3	27.2
45 to 50	7	3	42.9
50 to 55	4	1	25.0
55 to 60 and over	13	4	32.5

The chorea cases, however, show a striking difference in that the curve for heart involvement in the first attack is a reversal of the curve of age incidence. While chorea most frequently makes its appearance between the ages of five and ten years, the occurrence of heart disease here is lower than in any of the age groups in which it is found. Between the fifteenth and the twentieth years, on the

other hand, when chorea makes its appearance least frequently, the percentage of cases having cardiac complications is highest. The variation, however, is not great, ranging from 41.6 per cent in the five to ten year group to 50 per cent in the cases occurring between fifteen and twenty years. Further the observation is probably vitiated, to some extent at least, by the fact that the latter group comprised only 4 cases (Table III and Chart II).

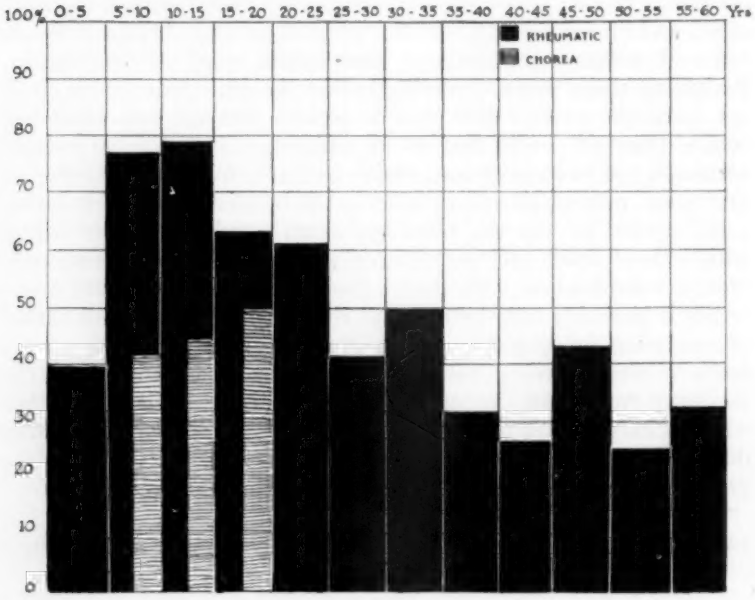


CHART II.—The incidence of heart disease in the first attack.

TABLE III.—INCIDENCE OF HEART DISEASE IN THE FIRST ATTACK OF CHOREA.

Age.	Total cases.	Cardiac involvement.	Incidence rate (per cent).
0 to 5	0	0	0.0
5 to 10	36	15	41.6
10 to 15	18	8	44.4
15 to 20	4	2	50.0

The literature dealing with this aspect of rheumatic infection presents rather a wide variation in the incidence rate. In an analysis of 244 first attacks of rheumatic fever Sir William Church[11] found that 75 per cent of the individuals under ten years had signs of cardiac pathology and that above this age evidence of these complications progressively diminished to 12.5 per cent after forty years. Poynton, Peterson and Spence[12] studied the incidence of heart disease in a group of children under twelve years. They found

it to be 44 per cent in 104 cases of chorea and 66 per cent in 172 cases of rheumatic fever. In a pathologic study, however, of 200 fatal cases of rheumatism Poynton, Agassiz and Taylor[13] found that of 100, who died under twelve years of age, 82 per cent had evidence of acute carditis, while in a similar number over this age acute carditis was present in only 45 per cent.

The statements previously made, that approximately 28 per cent of the rheumatic fever cases and 20 per cent of the chorea cases having cardiac involvement while in the hospital, showed evidence of progressing lesions when observed over a considerable period of time in the Follow-up Clinic, leads naturally to a question of fundamental importance. How long after the subsidence of the acute phase of the disease must one wait before having a reasonable certainty that potential cardiac damage has completely declared itself?

Twenty-five cases which were regularly seen in the Follow-up Clinic after discharge from the wards throw a certain amount of light on this question. In these the development of mitral stenosis was observed; 22 of them, or 88 per cent, showed well-developed physical signs within twenty-four months following the acute attack. Three of the cases, however, presented a striking time interval between the attack of acute rheumatism and the appearance of signs sufficiently definite to warrant a diagnosis of mitral stenosis. They were under more or less continuous observation and suffered no return of any acute rheumatic symptoms, yet one case showed none of the characteristic physical signs until a period of five and a half years had elapsed; in the second only at the end of six and a half years was the diagnosis of mitral stenosis possible. The third case, one of the chorea group, was similarly observed for five years, and eight months after the disappearance of the chorea before the typical signs of mitral stenosis were evident.

Although this lesion is demonstrable in the large majority of cases within a period of two years following the subsidence of clinically active disease, the fact that there are cases which require a much greater time interval implies the action of some factor other than simple adhesion of the valve leaflets and subsequent contraction of the mitral orifice. This is borne out by the not infrequent findings of Aschoff bodies in the heart muscle of persons dying after many years of complete freedom from symptoms of clinically active rheumatic disease. It would seem, therefore, that this infection may be both chronic and progressive and yet give little or no evidence of its presence for a period of years. Since this appears to be the case, the periodic examination of rheumatic patients, apparently cured, becomes of paramount importance. Even in the absence of arthritic phenomena repeated observations of temperature, leukocyte count and especially electrocardiographic studies are necessary to secure the guides to treatment which quiescent rheumatic infection emphatically demands.

The Role of Focal Infection. The frequent association of throat and tonsillar infection with acute rheumatic fever has led to much speculation concerning the possible role played by focal infection in the rheumatic syndrome. Of recent years the attempt has been made to attach to this condition a direct relationship with the etiology of rheumatic fever and the allied forms of this protean disease. Much has been hoped for, both of prophylactic and therapeutic value, from oral hygiene, removal of the tonsils and adenoids, and the eradication of other foci, which are available and amenable to treatment. It has been claimed that focal infection has a direct bearing upon both the chronicity and recurrent character of the disease through a mechanism as yet unexplained; but numerous investigators attacking this problem have published varying and, not infrequently, contradictory results.

To evaluate the relative importance of this factor it is necessary to have some knowledge of the incidence of focal infection in the general population. This was attempted by the study of a series of 400 cases, which gave neither history nor clinical evidence of any rheumatic condition. They were chosen at random from the files, but so selected that the distribution through the arbitrary age groups corresponded to that of the rheumatic fever series. Furthermore, only those case records were utilized in which the presence or absence of focal infection were specifically mentioned.

In both groups the tonsils were listed as infected when they were found to be swollen and inflamed, or to contain exudate within the crypts. Many of the rheumatic cases had tonsillectomy performed during their hospital period, and these were classified on the basis of the reports from the Pathology Department (Tables IV and V and Charts III and IV).

TABLE IV.—INCIDENCE OF FOCAL INFECTION IN THE CONTROL SERIES OF 400 CASES.

	Number of cases.	Incidence rate. (per cent).
Total cases having focal infection	268	66.6
Dental sepsis	157	39.2
Cervical adenitis	113	28.1
Tonsillar infection	110	27.5
Ears and nasal sinuses	6	1.5
Other foci	7	1.7
Tonsils previously removed	43	10.7

TABLE V.—INCIDENCE OF FOCAL INFECTION IN THE RHEUMATIC FEVER SERIES.

	Number of cases.	Incidence rate (per cent).
Total cases having foci of infection	317	80.6
Dental sepsis	183	36.8
Cervical adenitis	33	8.3
Tonsillar infection	231	58.8
Ears and nasal sinuses	10	2.5
Other foci	7	1.7
Tonsils present	319	81.4

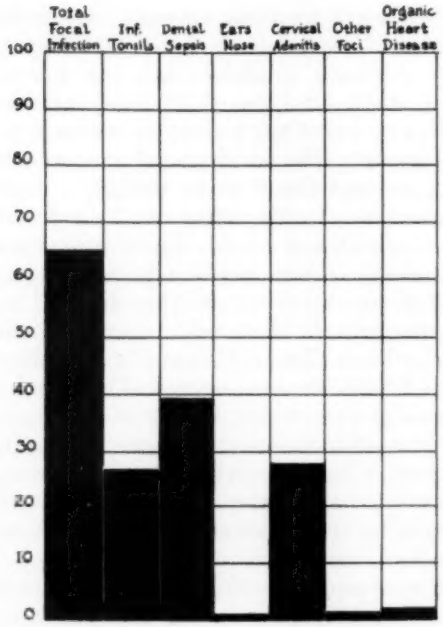


CHART III.—The incidence of focal infection in the control series.

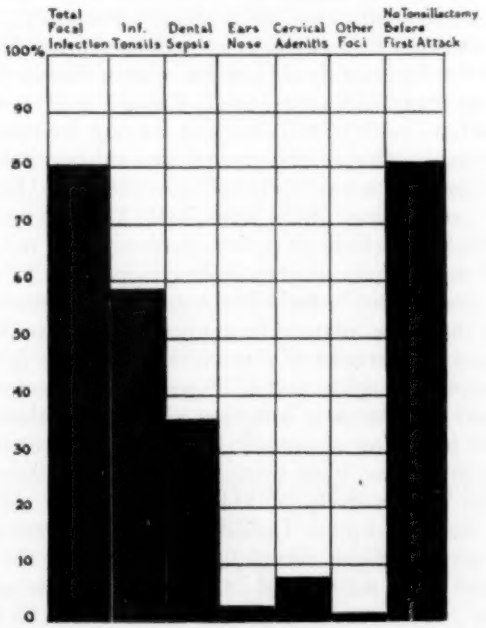


CHART IV.—The incidence of focal infection in the rheumatic fever series.

Comparison of the two groups presents some striking contrasts. Definite evidence of focal infection was found in 317 of the 393 rheumatic fever patients, a total of 80.6 per cent as against 66.6 per cent among the control group. Infected tonsils were present in 231, or 58.8 per cent, of the former, in contrast to 27.5 per cent in the control group. The incidence of the other types of focal infection, however, was found to be strikingly uniform, with the exception of cervical adenitis, which was considerably more frequent among nonrheumatic cases. These results seem to demonstrate that clinically evident foci of infection are more numerous among cases of rheumatic fever, and that diseased tonsils are more than twice as frequent in these cases than in a similar group of nonrheumatic patients (Tables IV and V). Lambert,[14] in a comparative study of 1000 consecutive cases of rheumatic fever and 250 consecutive cases of pneumonia, having no history of rheumatism or arthritis, found a much lower incidence of tonsillar infection in both groups, and a less marked difference between them. The variation, however, was in the same direction. His figures are 25.5 per cent among the rheumatic cases and 17 per cent among those having pneumonia.

Of late years the emphasis which has been placed upon recurrent sore throat and tonsillitis, as among the evidence of rheumatic infection, and possibly also as factors in the etiology of the disease, has led to a widespread adoption of tonsillar enucleation as a therapeutic, and occasionally as a prophylactic, measure. The interest which has attended this practice is evidenced in the literature of rheumatic fever by numerous articles which, however, not infrequently report contradictory results. Kaiser[15] analyzed two groups of school children, each 1200 in number, having the same indication for tonsillectomy. One of the groups was subjected to operation, while the other group was observed as a control. Both series of children were reëxamined three years later, and the findings at this time led him to conclude that tonsillectomy did not reduce the incidence of rheumatism, chorea or heart disease.

Ingerman and Wilson[16] studied two groups of rheumatic children to ascertain the value of tonsillectomy as a therapeutic measure. They observed recurrences of rheumatic symptoms in 76 per cent of the cases operated upon, and in 80 per cent of the control group. The definition of rheumatic infection adopted by these authors is a broad one, including rheumatic fever, chorea, cardiac valvular disease, growing pains, joint pains, myositis, sore throat and tonsillitis. Hunt,[17] in a study of 144 cases of acute rheumatism in children at Guy's Hospital, London, found recurrences in 53 per cent of 66 cases in which complete enucleation of the tonsils was performed and in 42 per cent of 78 cases which were not subjected to operation. St. Lawrence,[18] however, observed 85 children for an average period of three and a half years after complete removal

of the tonsils, all of whom had had acute rheumatic fever or chorea. During this interval only 16 per cent of the rheumatic cases had a return of the acute condition, while 50 per cent of the choreas showed renewed evidence of this condition. Of 58 cases of organic heart disease, 12 of whom had suffered at least one attack of decompensation before operation, only 1 developed cardiac insufficiency after tonsillectomy. He, therefore, concludes that "tonsillectomy (complete enucleation of the tonsils) would seem to be the most important measure at present available for the prevention of acute rheumatic fever and the allied rheumatic manifestations."

The results of tonsillectomy in the series presented here are not in keeping with those found by any of the writers quoted above. Two obvious explanations present themselves at once to account, in part at least, for this discrepancy. In the first place we are dealing with rheumatic fever and not the broad concept of rheumatic infection as defined by Ingerman and Wilson. Secondly, the cases fall into no particular age group but are comprised of both adults and children. In addition to tonsillectomy, every effort was made to find and correct other foci of infection before the patient was discharged from the hospital. The cases which were observed over a sufficient period of time have been grouped under three headings: Those who had tonsillectomy performed after the first or some subsequent attack; those who had no operation or only a partial removal of the tonsillar tissue; a small group of patients who had their tonsils removed before the first attack of rheumatism.

Eighty individuals whose tonsils were enucleated after an acute attack of rheumatism were observed over a period averaging three years and three months. Of them, 34, or 42.5 per cent, had recurrence of rheumatic fever. However, correction for the difference in the period of observation between the operated and unoperated groups, on the basis of the general incidence rate of recurrences, increases this figure to 48.9 per cent. Two hundred and seven cases, having had no tonsillectomy, or at most only a partial removal, were followed for a period averaging four years and five months. Of these, 125, or 60.3 per cent, suffered at least one return of the acute condition. The group of 12 patients whose tonsils had been completely removed before any evidence of rheumatic fever appeared, escaped recurrence. They were followed, however, for an average time of only one year and five months (Table VI and Chart V).

TABLE VI.—RELATION OF TONSILLECTOMY TO RECURRENCE.

	Complete tonsillectomy after first or later attack	No tonsillectomy.	Complete tonsillectomy before first attack.
Average time followed	3 yrs. 3 mos.	4 yrs. 5 mos.	1 yr. 5 mos.
Total cases	80	207	12
Number of recurrences	34	12	0
Incidence of recurrence	42.5%	60.3%	0

In a general way, it would appear from these figures that just as a high incidence of tonsillar infection accompanies the incidence of rheumatic fever when compared with a group of nonrheumatic controls, so the elimination of this potential source of disease seems to be associated with a fall in the rate of recurrences, other foci of infection being treated as well. However, it is pertinent to point out the necessity for close observation over a prolonged period of time before forming an opinion as to the merit of any prophylactic or therapeutic measure. As will be developed later, only 50 per cent of the cases having subsequent acute attacks develop them within a period of four years after the initial acute rheumatic fever.

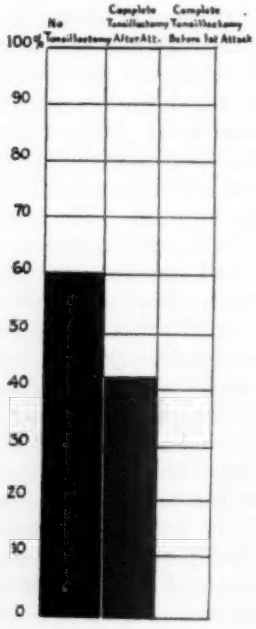


CHART V.—The relation of tonsillectomy to recurrence.

Recurrences of Rheumatic Fever. The tendency for the acute forms of this disease to recur after varying periods of quiet and apparent good health has long been recognized. It is this characteristic which renders prognosis so difficult; it is this which leads to so much of the progressive disability; it is with this knowledge that any approach toward the solution of the problem of rheumatism must be carried on. The frequency of recurrence, the expected time interval between the first attack and the first recurrence and the relationship, if any exists, between the incidence rate of later episodes and the age of the patient at the time of the onset of rheumatism, are facts necessary to a complete understanding of the disease.

Among the rheumatic fever series there were 252 cases available for analysis along these lines. They include only those individuals who gave in their histories an accurate date of the first attack of rheumatism, or those seen in the first attack and subsequently observed in the Follow-up Clinic for at least six months after discharge from the hospital. Of these, 180 individuals, or 71 per cent, irrespective of age, had at least one recurrence of acute rheumatic fever. The separation of the individuals into adult and child groups, depending upon the age at which the first attack occurred, again demonstrates the fact that age itself has an import-

CHART VI.—Comparison of the expected incidence of recurrences in children and adults.

ant bearing upon the development of the disease. The age of twenty was arbitrarily chosen as the dividing line. Of 87 cases comprising the adult group, 51, or 58.6 per cent, had recurrences. In the younger group of 165 individuals, 129, or 78.2 per cent, had at least one return of acute rheumatic fever (Chart VI and Table VII).

TABLE VII.—COMPARISON OF THE INCIDENCE OF RECURRENCE IN ADULTS AND CHILDREN.

	Number of cases.	Incidence (per cent).
Adults, age group over twenty years	87	58.6
Total cases with occurrence in the adult group .	51	
Children, age group under twenty years . . .	165	78.2
Total cases with recurrence in the child group .	129	

The distribution of these cases into groups according to the age at the time of the first attack, and the study of recurrence in these groups, again brings into prominence the importance of the age factor (Table VIII). Those cases occurring between the fifth and tenth years present the peak of the incidence rate of recurrences. Of 45 patients between these ages, 42, or 93.4 per cent, had a return of the acute phenomena. With two exceptions the curve follows a steady downward course in the later age groups, but it is not until after the age of thirty years that the incidence falls below 50 per cent. The secondary rises encountered in the two groups, twenty-five to thirty and forty to forty-five years, are probably due to the relatively small number of cases included. They emphasize, however, the fact that age does not confer immunity. With few exceptions, those individuals who experienced two or more recurrences fell among the cases whose initial attack of rheumatic fever occurred within the first twenty-five years of life (Chart VII).

TABLE VIII.—RELATION OF INCIDENCE OF RECURRENCE TO AGE AT FIRST ATTACK.

Age at first attack of rheumatic fever.	Total cases.	Recurrences.	Incidence (per cent).
0 to 5	11	5	45.4
5 to 10	45	42	93.4
10 to 15	67	50	74.5
15 to 20	42	32	76.2
20 to 25	34	22	64.6
25 to 30	14	12	85.8
30 to 35	11	5	45.5
35 to 40	14	6	42.8
40 to 45	4	4	100.0
45 to 50	4	0	0.0
50 to 55	1	0	0.0
55 to 60 and over	5	2	40.0

The attempt to ascertain the average time interval between the initial attack and the first recurrence, as already mentioned, revealed the surprising fact that only 57 per cent had the first recurrence within four years after the primary episode. The incidence of recurrence in the 144 cases available for study was found to be 23.6 per cent within one year, 38.8 per cent within two years, 52 per cent within three years and 56.8 per cent within four years, while a total of 43 per cent waited four years or longer before the first secondary attack of acute rheumatism occurred. It would appear, therefore, that it is only after the lapse of three years of complete freedom from symptoms that an individual has better than an even chance of escaping a further bout with acute rheumatic fever (Chart VIII and Table IX).

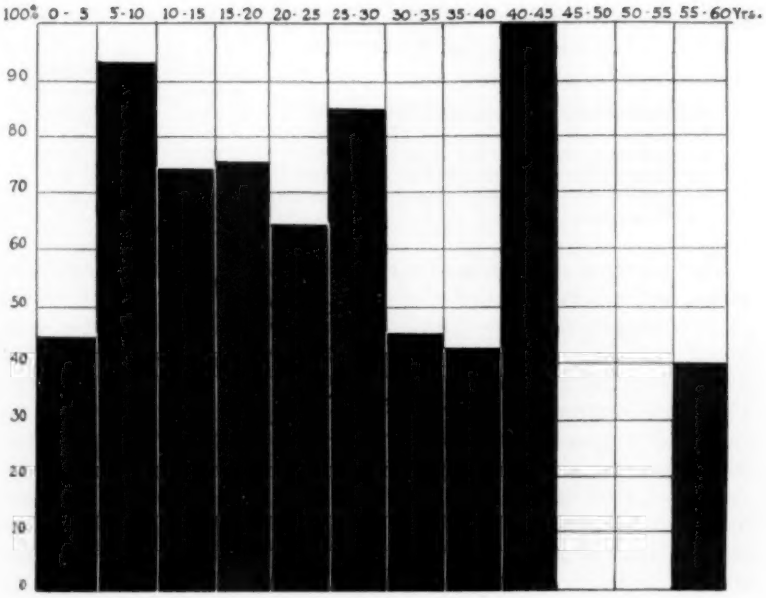


CHART VII.—Relation between age at time of first attack of rheumatic fever and incidence of recurrences.

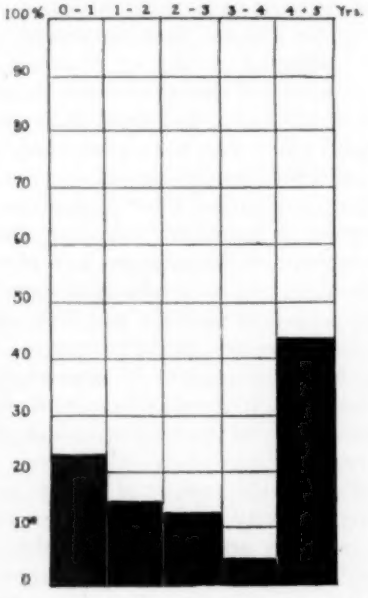


CHART VIII.—The time interval between the first attack of rheumatic fever and the first recurrence, expressed in years.

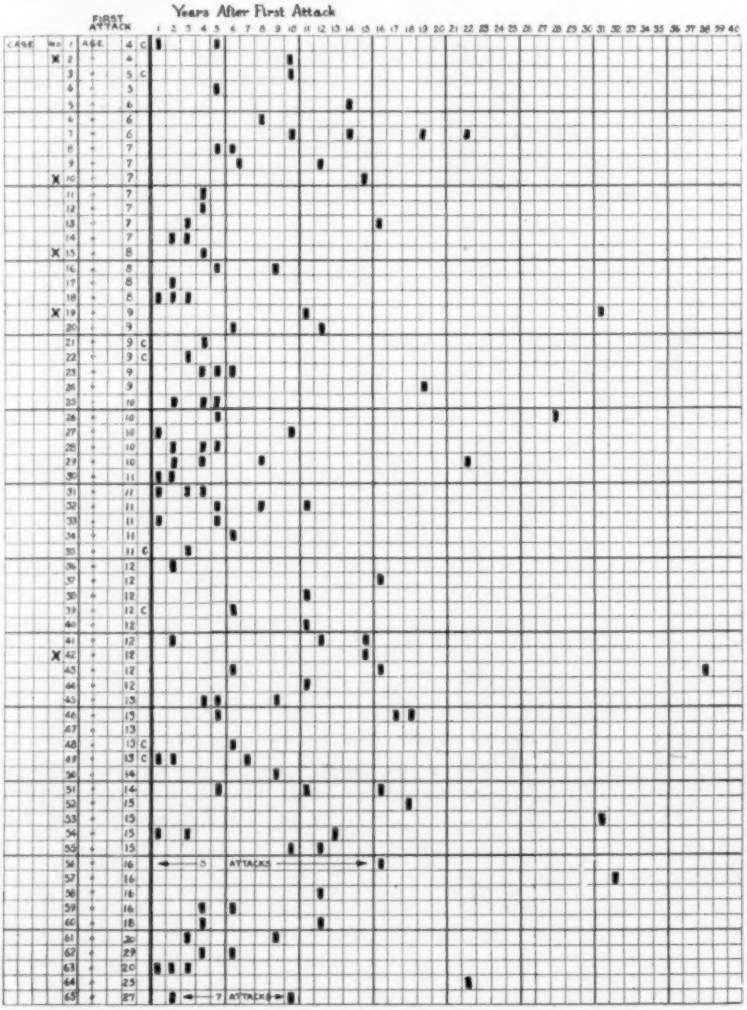
TABLE IX.—INTERVAL BETWEEN THE FIRST ATTACK AND THE FIRST RECURRENCE.

	Number of cases.	Incidence (per cent).
Recurrence within one year after first attack . .	34	23.6
Recurrence between one and two years after . .	22	15.2
Recurrence between two and three years after . .	19	13.2
Recurrence between three and four years after . .	7	4.8
Recurrence more than four years after first attack	62	43.2
Total cases	144	

The selection of 65 cases from among those giving accurate histories, and others observed over a period of several years, illustrates in a striking fashion the chronic course which rheumatic fever may run (Chart IX). A large number of these individuals have had a return of acute rheumatic fever ten years after the initial attack. There are scattered cases which show recurrences after fifteen to twenty-five years, and in 4 acute rheumatism reappeared after more than thirty years. Case VII had the first acute attack at six years and four subsequent attacks respectively ten, fourteen, nineteen and twenty-two years later. Case 19 was nine years of age at the time of his first rheumatic fever. After repeated minor attacks in the interval he had a second bout with acute rheumatism eleven years later and again thirty-one years after the initial episode. Case 43 developed rheumatic fever at twelve years, and three other attacks, respectively, six, sixteen and thirty-eight years later. When it is recalled that the cases dealt with include only the acute polyarthritic type of the disease, that recurrences only of this type were studied, the potential threat of rheumatism gains added importance, for it is conceded that the disease manifests itself under many other forms, much less well-defined clinically.

Much of the data which has been presented leads one almost inevitably to the conviction that rheumatic fever cannot be regarded as an acute infection terminating after a longer or shorter interval. It is probably incorrect to regard the secondary attacks as a simple reinfection. The concept of rheumatism as a chronic, slowly progressing disease characterized by intervals of calm simulating complete recovery, and periods of activity which entail further damage to the organism, seems more accurately to correspond with observed phenomena. It is highly important to appreciate, moreover, the fact that these periods of activity may present a very varied picture both as regards the severity of the subjective and objective findings, and especially as regards their prognostic import. The picture of rheumatism comprises a wide variety of conditions differing markedly in their apparent gravity, yet all too frequently such evidence as growing pains, a slight anemia with an almost imperceptible elevation of the white blood count and temperature are followed by damage fully as severe as that attending upon chorea or an acute polyarthritis.

As has been pointed out already, it has long been known that lesions occurring in this disease differ characteristically in children and adults. Among the former an acute multiple joint involvement with swelling, effusion, increased heat and redness, acute tender-



× Repeated attacks in interval. ▮ Attacks of acute rheumatic fever.

CHART IX.—Chronicity of rheumatic disease.

ness and pain, relatively high fever and leukocytosis, is much less frequent. The disease as seen characteristically among them often produces relatively little immediate disability. Occasional slight muscle pains, occasional attacks of "sore throat" or a slight per-

sistent anemia may be the only superficial warnings of a process of the utmost gravity. The picture of a child some years or months after an attack of rheumatic fever or chorea, dying of heart failure, but without evidence of nervous or arthritic phenomena, is not an unfamiliar one. It is important to emphasize the fact that reduction in the exercise tolerance and the beginning of cardiac insufficiency are preceded in all cases by an elevation of temperature, perhaps only a fraction of a degree above normal, and by leukocytosis often little above the level of health. To a lesser extent, probably the same undoubtedly holds true in adults.

The importance of repeated observation of the patient is evident. The fact that only 57 per cent of the recurrences of acute rheumatism occur within a period of four years demands that this observation be a prolonged one. The development of serious complications during an interval of quiet, so far as regards the more striking manifestations, requires that observation be detailed and careful. In this respect repeated temperature readings, blood counts and, when possible, electrocardiographic examinations are essentials in the proper after care of the individuals suffering from rheumatic infection.

The cases seen in a general hospital roughly fall into two groups: one comprised of individuals with a recent onset of rheumatism and presenting signs of comparatively little severe visceral damage; the other, of many persons who enter in the late stages of the disease, perhaps years after its onset, with extensively damaged hearts, often completely decompensated. Of these latter, there are some who may look forward to a few years more of activity, much limited however, but many have no future to anticipate other than that of being a burden to themselves, to their families and to the community. It is very questionable whether this state of things is a necessary contingency upon rheumatic infection. Probably by far the largest portion of individuals suffering from this disease receive little or no intelligent care, for both the potential chronicity and the evidence of low-grade activity often pass unrecognized and untreated. In this respect the use of salicylates has proved to be a not unmixed blessing. It is a now generally accepted fact that their action is probably in no sense specific for the disease, and that their value lies solely in their ability to produce symptomatic relief. Because of this action, especially in the subjectively milder forms of rheumatic infection, the administration of salicylates confers a false sense of security. In the hospital where observation is close this potential danger is of less importance, but among ambulatory cases the action of salicylates may completely mask the warning signals of progressing disease.

Garrod,[10] in 1890, said: "The recurrent attacks of rheumatism, differing so widely in their characters . . . present certain analogies with the phenomena of syphilis." Recently Swift[19] has

emphasized the similarity of rheumatism to both syphilis and tuberculosis, and has stressed the essential feature of the treatment of rheumatism, prolonged rest and frequent observation.

It is interesting to contrast the prevalent ideas and methods of treatment in these three diseases. Prolonged observation of the patient, repeated intensive courses of therapy and frequent Wassermann tests are admittedly essential in the attempt to arrest the progress of luetic infection. Limitation of activity, proper hygienic surroundings, suitable diet and repeated studies by Roentgen ray examination are necessary for anything like a successful assault upon tuberculous disease. The great numbers of sanatoria for the treatment of tuberculosis are evidence alike of the rationale of this regime and of the responsibility of the community in the effort to combat its spread. Yet rheumatism, which properly belongs with these two diseases as a source of economic loss, is regarded in a wholly different light. The frequent findings of multiple cases in the family group, and the reports of outbreaks almost epidemic in character among troops during the World War, point strongly toward the probability that rheumatism is an infectious disease. Further evidence of a similar nature is supplied by the results of comparative studies of rheumatism and tuberculosis which have shown a striking parallel in the incidence of 2 or more cases within the family group.[20]

Despite these striking analogies, however, relatively little progress has been made in the problems of care and prevention of rheumatic disease. The importance of prolonged and careful observation of the patient during the periods of quiescence is not generally appreciated. The necessity for prolonged rest under medical care in suitable surroundings is not realized. The community which provides so well for the arrest of tuberculous disease, and the rehabilitation of the patient, offers no help to the victim of rheumatism until the late stages of the disease have supervened and the road to health and economic independence has been closed. Further attack upon the problem of rheumatic infection must be directed not only to the discovery of the etiology of the disease, but to the education necessary to provide the means for its adequate and successful treatment.

Summary. 1. Rheumatic fever in approximately 70 per cent of all cases, irrespective of age, presents itself as a chronic disease, characterized by periods of recurrence of the acute features—fever, arthritis and leukocytosis.

2. The age of the patient is a highly important factor in the prognosis. This is evident from the fact that under the age of fifteen years is found the highest incidence of first attacks, of cardiac involvement and of liability to recurrence.

3. Serious cardiac involvement occurs in 68 per cent of cases irrespective of age. Between the ages of ten and fifteen years

approximately 78.2 per cent of all cases present evidence of this complication in the first attack, and only after the age of twenty-five years does the incidence of heart disease fall below 50 per cent in the initial attack of rheumatic fever.

4. That focal infection plays a role in the etiology seems apparent from a comparison of its occurrence in the rheumatic cases, with a series of 400 nonrheumatic controls. In the former group it was found in 80 per cent of individuals as against 66 per cent in the latter group. Tonsillar infection was found to be more than twice as prevalent in the rheumatic fever cases as in 400 nonrheumatic controls.

5. The complete removal of the tonsils when evidence of infection is present, together with appropriate treatment of other foci of infection seems to reduce but not to remove the incidence of recurrences of rheumatic fever.

6. The expected incidence of recurrences in all age groups was found to be 71 per cent. In patients above the age of twenty years, at the time of the first attack of rheumatic fever, it was found to be 58.6 per cent, while below the age of twenty the incidence rate was 78.2 per cent.

7. In a general way, the younger the patient at the time of the first attack of rheumatism, the greater is the probability of recurrence; 93 per cent of all cases having the first attack between the fifth and tenth year have recurrences of the acute condition.

8. Only 57 per cent of the first recurrences were found to develop within a period of four years following the first attack of rheumatic fever. This would seem to be a very important factor in analyzing the true worth of any therapeutic or prophylactic attack upon the problem of rheumatism.

NOTE.—I wish to express to Drs. George M. Mackenzie, A. R. Dochez, and William St. Lawrence my appreciation of their suggestions and helpful criticism as to the collection and arrangement of the data presented in this paper, and to Dr. Walter W. Palmer for permission to use the Presbyterian Hospital records.

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THE SIGNIFICANCE OF AMPHORIC BREATHING AND COIN SOUND TEST, WITH ESPECIAL REFERENCE TO THEIR PROGNOSTIC VALUE.

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Amphoric breathing and the coin or bell sound have long been considered as the most characteristic signs of pneumothorax, though their absence by no means excludes this affection. James[1] found the amphoric phenomenon to be present in about one-third of all cases of spontaneous pneumothorax, and according to Emerson[2] it was found in more than 50 per cent of cases.

I have examined more than 200 cases of artificial pneumothorax repeatedly at Bedford Hills and the Jewish Consumptives' Relief Society Sanatoria for tuberculosis and was amazed not to find amphoric breathing in any of these cases, irrespective of the intrapleural pressures created, whether negative or highly positive. However, it was heard for certain periods of time in those cases in which a spontaneous pneumothorax developed during the course of pneumothorax therapy, and in primary spontaneous pneumothorax which were or were not maintained artificially by reinsufflations, that is, it was present in all cases of the so-called pneumogenic pneumothoraces. The coin tap test, on the other hand, was elicited in all cases of pneumothorax, spontaneous as well as artificial, in which the intrapleural pressures were at or above the atmospheric one, regardless of whether the pneumothoracic cavity was large and complete from apex to base, or only small and localized.

These observations indicated clearly that amphoric breathing

was not due only to the presence of air in the pleural cavity, but to some other cause which marked the fundamental difference between spontaneous and artificial pneumothorax, and that the coin sound had a different significance than the amphoric sound.

Before going into discussion of the mode of production, diagnostic significance and prognostic value of these signs, I want to report briefly a few illustrative cases of spontaneous and artificial pneumothorax as well as of large pulmonary cavities with particular reference to their various auscultatory findings.

Report of Cases. CASE I.—(Figs. 1 and 2.) Male, aged twenty-two years, was given pneumothorax treatment because of an active tuberculous lesion of right lung. Three hundred cubic centimeters of air were given at initiation. One hour later the patient began to complain of dyspnea and tightness in the right chest. Physical examination of the chest revealed hyperresonance of the entire right hemithorax, a high echoing bell sound and the most exquisite amphoric sound from the third rib down, heard anteriorly, posteriorly and axillary region. The point of maximum intensity of the amphoric sound was in the midaxillary line at the fourth interspace where the needle was inserted. A roentgenogram taken the same day disclosed a right spontaneous pneumothorax extending from apex to base (Fig. 1). The amphoric breathing disappeared after five days, while the coin sound persisted until the ninth day. Roentgenoscopic observations showed a gradual reëxpansion of the lower lobe particularly (Fig. 2, a Roentgen ray plate taken ten days later). He has been given many reinflations in the amounts of 500 to 600 cc. of air, but never since have we obtained the coin sound or amphoric breathing.

CASE II.—(Figs. 3 and 4.) A woman, aged forty years, was given artificial pneumothorax on the right side for several months. The pneumothorax extended from the apex to about the fourth rib leaving the lower portion of the lung unaffected (Fig. 3). There was slight tympany over the pneumothorax area, and absent breath sound. There was harsh vesicular breathing from the fourth rib down anteriorly and posteriorly. No coin sound could be elicited. The refills in quantities of 400 to 500 cc. of air were always given with the needle in the third interspace. To effect compression of the lower lobe the needle was introduced in the fifth interspace and anterior axillary line. Manometric readings indicated that the needle was in the lung. The needle was gradually withdrawn and negative readings were obtained. Five hundred cubic centimeters of air were injected. About six hours later the patient complained of heaviness and pain in the right side of the chest. Percussion revealed a tympanitic sound from apex to base, more marked in the upper half. The coin sound was musical and

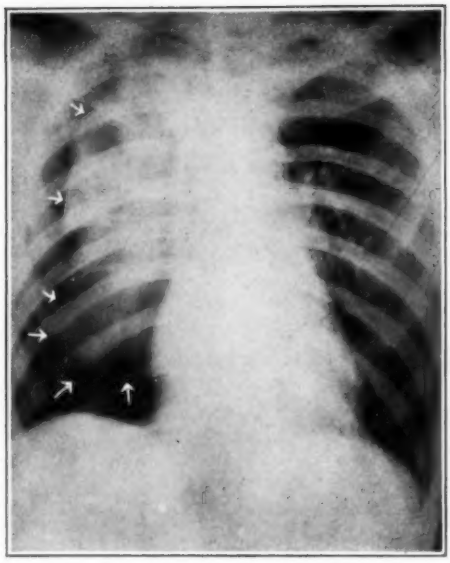

FIG. 1.—Right spontaneous pneumothorax developed after introduction of 300 cc. of air. Intrapleural pressures are positive. Exquisite amphoric breath sound and bell sound are present.

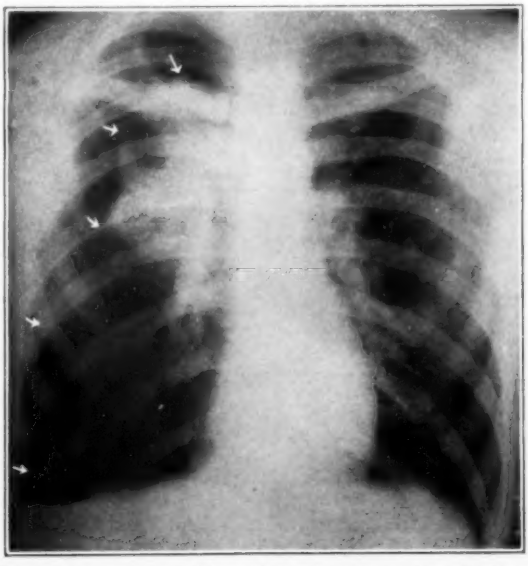

FIG. 2.—Plate of same case as Fig. 1 taken ten days later. Note reëxpansion of lower lobe. Intrapleural pressures are negative. Neither amphoric breathing nor coin sound are present.

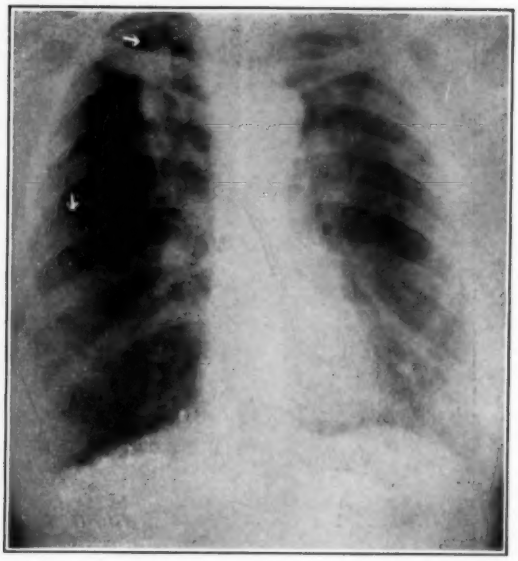

FIG. 3.—Right artificial pneumothorax extending from apex to fourth rib. Amphoric breathing never elicited. Coin sound present only when intrapleural pressures are positive.

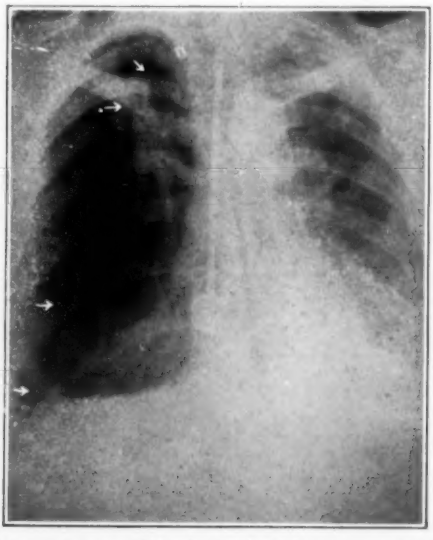

FIG. 4.—Plate of same case as Fig. 3 one day after a spontaneous pneumothorax supervened upon the artificial pneumothorax. Amphoric breathing with maximum intensity at fifth interspace anteriorly, where the manipulating needle was inserted. Coin sound is chime like.

FIG. 5.—Left hydropneumothorax. Existence of pleurobronchial fistula proven by injection of gentian violet. Inspiratory and expiratory blowing amphoric breath sound. Coin sound feeble. Metallic tinkle when fluid level reaches fifth rib.

FIG. 6.—Right localized pyopneumothorax with definitely established bronchial fistula. Amphoric breathing appears and disappears with change of fluid level. Coin sound absent.

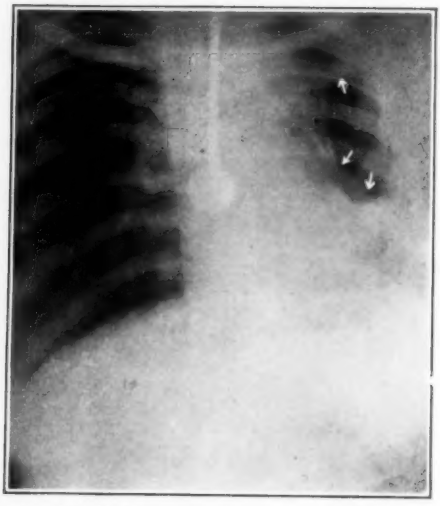

FIG. 7.—Left localized artificial pneumothorax extending from second to fifth rib. At no time was there amphoric breathing elicited. Coin tap sound present after each reinflation when intrapleural pressures are positive.

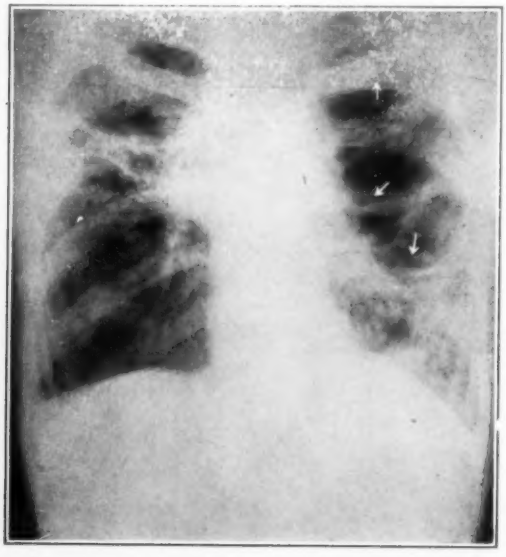

FIG. 8.—Large left pulmonary cavity extending from apex to fourth rib. Amphoric breathing and metallic tinkling heard occasionally in the morning when cavity is not drained. Coin sound of very low pitch elicited at times.

ringing. Sharp amphoric breating was heard best at the fifth interspace and anterior axillary line. A roentgenogram showed a pneumothorax from apex to base compressing most effectively the upper lobe (Fig. 4). The amphoric sound disappeared in two days; the bell sound was persistent. Five days later the intrapleural pressures were found to be + 40 + 20 mm. (water manometer). The patient has been given many refills but no amphoric breathing was ever heard; the coin sound was occasionally obtained immediately after the refill if the intrapleural pressures created were at, or above the atmospheric pressure.

CASE III.—(Fig. 5.) Spontaneous pneumothorax developed during the course of pneumothorax therapy on the left side in a man, aged forty years. Later on pyopneumothorax ensued. Gentian violet was injected into the pleural cavity and appeared in the sputum a few minutes later, which confirmed beyond doubt the existence of a bronchial fistula. A low-pitched blowing amphoric breath sound was heard in inspiration and expiration. No coin sound was ever elicited. The amphoric breathing was audible all along, its pitch growing higher as the level of the fluid rose in the chest. When the fluid reached the fourth interspace no amphoric sound could be heard. After drainage, postural or by aspiration, the amphoric breathing reappeared. At times, when the fluid level was at about the fifth rib, faint metallic tinkling was audible on cough.

CASE IV.—(Fig. 6.) Patient was admitted to the sanatorium as an emergency case because of marked dyspnea, severe pain in right side of chest, pyrexia, and general malaise. He gave a history of having experienced a sudden severe pain in the right chest after which he coughed up about 10 ounces of mucopurulent material. Auscultatory examination disclosed a blowing amphoric breathing, heard loudest at midaxillary region and fourth interspace. A roentgenogram showed a small right spontaneous pneumothorax. The intrapleural pressure was the same as atmospheric, and gentian violet injected into the pleural cavity appeared in the sputum within one minute. No coin sound was obtained over this pneumothoracic area. The amphoric breathing disappeared when the cavity filled up, but when the level of the fluid was at the fifth rib a distinct metallic tinkling was heard on inspiration.

CASE V.—There was small left-sided artificial pneumothorax extending from first to fifth rib (Fig. 7). No breath sounds were heard over this area. After the introduction of 200 cc. of air the intrapleural pressure rose to + 40 + 60 mm. (water manometer). Coin sound was high pitched and heard anteriorly and posteriorly for about four days after the reinflation. The intrapleural pressure

before the injection of air was − 50 − 20 mm. (water manometer). As soon as the intrapleural pressure became positive the coin sound reappeared. At no time was there amphoric breathing present.

Case VI.—There was a large pulmonary cavity extending from the apex to about the fourth rib (Fig. 8). Cavernous breathing and moist bubbling rales were heard over this area anteriorly and posteriorly. Amphoric quality of sound obtained at times in the morning. Occasionally metallic tinkling was present on coughing, particularly in the morning when the cavity had not been drained. A low-pitched coin sound was elicited at times.

Discussion. The mode of production of amphoric breathing has long been the subject of debate among the best of clinicans and as yet no unanimity of opinion has been reached. Laënnec,[3] Williams,[4] and Weil[5] are of the opinion that a bronchial fistula is one of the prerequisites for the production of amphoric phenomena, whereas Skoda,[6] Marais,[7] Hoover,[8] and Emerson[2] consider amphoric breathing simply as an intensified tracheal or cavernous breathing, the pneumothoracic cavity acting just as a resonance chamber which by its selective action in responding to certain overtones and not to others changes the quality of the sound.

The theory advanced that pneumothorax is simply a resonance chamber intensifying a sound produced in an adjacent cavity or in the trachea loses all its ground in the light of the physical signs in artificial pneumothorax which as I indicated in another contribution[9] are of several types. In none of these types of pneumothorax was there ever an amphoric quality to the breath sounds; neither in the expansile type of pneumothorax in which the intrapleural pressures were always negative, and the collapsed lung continued to expand and contract with each respiratory phase; nor in the static pneumothorax where the intrapleural pressure was at about the atmospheric one, and the lung was at rest; nor in the compression pneumothorax in which the positive intrapleural tension reached at times as high as + 30 + 40 mm. of mercury, and the lung volume was reduced to its minimum; nor in any localized pneumothorax irrespective of the pressures created in it. The size of the pneumothoracic cavity had, therefore, nothing to do with the production of amphoric breathing; neither could the continuous function of the collapsed lung be considered a factor, nor could the intrapleural tension alone explain its mode of production.

On the other hand amphoric breathing was always present in cases of artificial pneumothorax in which a spontaneous one supervened, as well as in all cases of primary spontaneous pneumothorax, whether complete from apex to base or only localized. This amphoric breath sound lasted from one day to a few months and its intensity was modified not only in different cases but also in the same case

at various times. Whenever the amphoric quality of the breath sounds disappeared the affected lung began to reëxpand gradually but persistently as could be observed carefully by roentgenoscopy. Case I is very illustrative in this respect. Case II is another illustration that amphoric breathing is provoked by a perforation in the visceral pleura. Cases III and IV, in which bronchial fistulæ were proven beyond doubt and amphoric breathing was heard both during inspiration and expiration, are other examples of the relation of a visceral pleural opening and the production of amphoric breathing.

It is interesting to note that in those cases in which amphoric breathing was audible only during inspiration it disappeared much sooner than in those cases where it was heard both in inspiration and in expiration. The impression was also gained that an inspiratory and expiratory amphoric sound was present only in cases with a definite bronchial fistula or where the perforation occurred in an infiltrated and indurated pulmonic area, whereas if the perforation was caused traumatically by the manipulating needle, particularly if it occurred in a portion of nondiseased lung tissue, an amphoric sound was heard only in inspiration. This was probably due to contraction and compression of the healthy elastic lung tissue during expiration closing the pleural perforation, while if the aperture was of sufficient size and in an indurated area, it could not be closed entirely even during expiration, allowing the air to enter through it from the pleura into the lung and this no doubt imparted to the breath sound an amphoric quality.

Very often an amphoric sound could be elicited only after coughing. This might be explained by a high intrapleural tension which keeps the lung perforation closed, but on coughing the intrapulmonary pressure increases and causes a forceful ingress of air into the pneumothoracic cavity through the pleural opening. This is very often the case in the so-called valvular pneumothorax. One case of a right-sided spontaneous pneumothorax is of especial interest in this respect. All the mediastinal structures were pushed over to the left side. A roentgenogram showed the entire lung collapsed, hanging in the form of a large pear near the mediastinum. The coin sound was chimelike, but no breath sounds were heard at all. The intrapleural pressures were + 20 + 14 mm. (water manometer). After the removal of 1000 cc. of air from the pleural cavity, the pressures became 0 + 8, but there was no change in the physical signs except for an exquisite amphoric sound on coughing which was no doubt due to the reopening of the viseral pleural fistula as a result of the diminution in the intrapleural pressure, and inflow of air through it. In all the cases of artificial pneumothorax uncomplicated by a spontaneous one, cough will never bring out the amphoric phenomenon.

The question then arises where is the origin of the amphoric

sound? Without going into detail of discussion as to the mode of production of breath sounds in general, it might be stated that two views prevail: (1) That it is produced in the larynx; (2) that it originates in the chest. Chauveau[10] and others seem clearly to have established the fact that experimental obliteration of the glottic sound does not anul the inspiratory sound heard by auscultation over the lung, hence he believes that it originates in the chest itself. Bushnell,[11] on the other hand, seems to have proven experimentally that all breath sounds are produced in the larynx, but are modified by conduction and sympathetic vibrations of the resonators of the lung tissue and thoracic cavity. Neither of these views alone can explain the production of amphoric sound. It certainly cannot be considered as a sound originating in the larynx or trachea and simply being reinforced by the resonance of the pneumothoracic cavity, because then we should hear it in all cases of pneumothorax in which laryngeal and tracheal breathing are never obliterated. The assumption that pneumothorax is a resonance chamber intensifying a sound produced in a neighboring cavity is altogether untenable, inasmuch as it was never heard in cases of artificial pneumothorax though large cavities and definite cavernous breathing were present, while it was distinctly audible in cases of spontaneous pneumothorax in which there was no evidence of cavitation. Furthermore the size of the pneumothorax resonance chambers has evidently little to do with the production of amphoric breathing, since we hear it in large as well as in small pneumothoraces. Barlow and Thomson[12] have heard it in small localized pneumothorax, and I heard muscial amphoric sounds in a case of spontaneous pneumothorax not larger than 3 or 4 inches, as was revealed by a Roentgen ray plate. These observations all seem to point to the fact that the amphoric sound is produced by the entrance of air into the pleural cavity through the perforation, setting up vibrations in the enclosed air of the pneumothorax as well as the thoracic wall. It is upon these vibrations that the volume, quality and intensity the amphoric sound depend. It seems also that the higher the intrapleural tension and the more forceful the inrush of air into the pleural cavity the more intense and more musical is the amphoric sound. This does not mean that amphoric breathing is produced wholly at the perforation; there might also be in it a laryngeal element, but its amphoric quality is imparted to it, when it passes through the visceral pleural opening, possibly due to the vibration of the lips of the opening which in turn set up sympathetic vibration in the column of air in the pneumothorax. The closed pneumothorax cavity *per se*, however, seems to be rather a poor resonance chamber as far as the breath sounds are concerned.

Is amphoric breathing heard best at the site of the visceral pleural perforation? This question cannot be answered with certainty, though in all the cases where the spontaneous pneumo-

thorax was evidently caused by the manipulation needle, the intensity of the amphoric sound was greater around the site of the puncture. Since the size of the perforation could not be bigger than the caliber of the needle used, which was of a very small size, the amphoric sound could be elicited only on deep inspiration. As a rule the amphoric breathing disappeared in a few days. In every case of pneumothorax in which amphoric breathing is audible there is an area of maximum intensity and this area could perhaps be considered as the point of the visceral pleural perforation. In this connection it might be of interest to note that whenever metallic tinkling is heard in cases of hydropneumothorax, its point of maximum intensity is at the level of the fluid. This might be caused by the inrushing air through the fistula at the fluid level, setting up waves on its surface which in the presence of air produce that peculiar metallic tinkling. Case III is corroborative of this hypothesis; whenever the fluid reached a higher level the metallic tinkling disappeared, due perhaps to the closing of the fistula by the accumulated fluid, but when the fluid was aspirated to a lower, level metallic tinkling reappeared. The assumption that metallic tinkling is due to reverberating rales in a neighboring cavity seems erroneous, in view of the fact that we have never heard it in cases of pneumothorax unassociated with fluid though moist bubbling rales were heard over the collapsed lung. On the other hand metallic tinkling was occasionally heard in pulmonary cavities, particularly in the early hours of the morning before the patient had time to drain the cavity.

It is of clinical interest to note here that pure amphoric breathing such as heard over a pneumothoracic cavity was seldom if ever heard over a pulmonary cavity. It seems that a clear distinction between cavernous and amphoric breathing is to be established, and should never be confused. The cavernous sound is hollow, blowing in character, low pitched and lacks the *musical quality* of the amphoric sound. It is always heard on inspiration and expiration, whereas amphoric sound is usually heard best on inspiration. Only a large bronchial fistula which communicates with a small pneumothoracic cavity gives rise to a respiratory sound which is cavernous-amphoric in character, that is, low pitched and blowing but with a musical note of an amphoric quality. On the other hand, there are many large pulmonary cavities which never give rise to cavernous breathing. Dr. C. T. Burnett and I are making a study of these so called "silent" cavities and we find that quite a few of these are entirely mute, that is exhibit no breath sounds at all, the same as in cases of closed pneumothorax. This is no doubt due to a closure of the bronchus which does not permit the air to enter the cavity. The cavernous tinge seems to be imparted to the breath sound only when the air enters the cavity through an open bronchus. The reasons why the breath sounds of a pulmonary

cavity usually lack the amphoric quality may be various: The size of the bronchial opening into the cavity is usually of a larger caliber than in the lung perforation of pneumothorax; the pressure in the cavity is never above atmospheric; a cavity is usually surrounded by other lung tissue which muffles the sound, even in the most superficial cavity the walls are much more thickened than in pneumothorax, inasmuch as in such cases there are marked synechiæ between the visceral and parietal pleura which are thickened and fibrosed and do not respond to vibration as readily as does the thoracic wall; the opening of the bronchus is smoother and firmer than the vibratory mouth of the lung perforation in pneumothorax which might act in the same way as the lips of an organ pipe to the inrush of air. The metallic tinkling heard occasionally in a pulmonary cavity might be explained as being produced by the waves stirred up in its accumulated secretion through the ingress and egress of air with each respiratory phase. Case VI lends support to this view.

The coin or bell sound is an auscultatory percussion sign elicited by tapping a coin sharply against another held firmly in contact with the chest wall while listening with the stethoscope at the opposite wall of the affected side. The impact of the two coins is heard as an echoing metallic ring, not unlike the distant sound of a chime of bells. The intensity of the sound bears more relation to the intrapleural pressure than to the size of the pneumothoracic cavity. Case V is very illustrative in this respect; no coin sound was ever obtained when the intrapleural pressure was negative, but after the injection of 200 cc. of air creating a positive pressure a beautiful coin sound could be elicited. This phenomenon is to be explained probably by the more frequent vibrations of the gas under tension. It is a well-known physical law that in cases of two strings of the same length and mass per unit length, the frequencies of vibrations are proportional to the square roots of the tensions. An increase in number of vibrations means also an increase in pitch. Its quality, on the other hand, varies with the size of the pneumothoraxic cavity, being more ringing and reverberating the larger the cavity.

Coin sound was also audible over large superficial pulmonary cavities, but in such cases it resembled more the distant sound of a hammer and anvil. A coin sound of the same quality is obtained over pneumothorax in which the intrapleural pressure is at about the atmospheric.

In cases of spontaneous pneumothorax in which amphoric breathing is absent and the coin sound is intensely echoing, a high intrapleural tension is always to be found. A gradual decrease in the intensity of the bell sound indicates a diminution in intrapleural pressure and a slow reëxpansion of the collapsed lung.

In cases of hydropneumothorax the bell sound assumes a higher

pitch and of shorter duration as the level of the fluid rises high in the chest; it also alters its pitch with the change of the position of the patient. Such postural changes have little effect on the bell sound heard over a pneumothorax with a high intrapleural tension.

Conclusions. Amphoric breathing denotes not only the presence of pneumothorax, but it also indicates a perforation in the visceral pleura of the collapsed lung; it can therefore be used as a differential sign between an open and closed pneumothorax. The intensity of the amphoric sound varies with the size of the pleural opening, the intrapleural tension and the depth of respiration. A blowing amphoric sound lasting for a long period of time is of poor prognosis; it denotes a persistent bronchial fistula inhibiting the reëxpansion of the collapsed lung. The disappearance of amphoric breathing is of good prognosis provided no fluid has developed in the pleural cavity; it indicates closure of the pleural perforation and that consequently a reëxpansion of the lung is to follow.

Amphoric breathing is also present occasionally in large pulmonary cavities, but it seldom possesses the same musical quality and pitch, and as a rule moist bubbling rales are present, due to the secretion in the cavity.

The coin sound is heard over open as well as closed pneumothorax, but its pitch is higher the higher the intrapleural pressure, and is more echoing the larger the size of the pneumothorax. It is also heard occasionally over large superficial pulmonary cavities but is of a low pitch and less musical.

In case of spontaneous pneumothorax in which amphoric breathing is absent and the coin sound is ringing and reverberating, a high intrapleural tension is to be suspected. The gradual recession in the pitch of the coin sound indicates a decrease in the intrapleural pressure and a slow reëxpansion of the collapsed lung.

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ACUTE OMENTOVOLVULUS.

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Acute intra-abdominal torsion of the omentum is a rare condition. Since Marchetti, in 1851 reported the first case, many contributions have been made to the literature on this subject. Most of the reported cases, however, were associated with some readily recognized inflammatory condition or with a hernia. The relation to hernia is striking, the right inguinal variety predominating.

Vignard and Giraudeau reported 20 cases of torsion, inguinal hernia being present nineteen times. Stewart found a hernia in 28 of 33 cases investigated by him. Corner and Pinches report 47 herniæ present in 53 cases. In no instance was a femoral hernia present.

On a purely anatomic basis Payr (quoted by Wilensky) divided all cases into the following groups:

1. Torsion without co-existing hernia.
   (*a*) Omentum alone involved.
   (*b*) Omentum and adherent viscera involved.
2. Torsion with co-existing hernia.
   (*a*) Of intra-abdominal portion of omentum only.
   (*b*) Of hernial portion only.
   (*c*) Combination of both.

The torsion may be single, double or multiple. When single, it is usually in a hernial sac, and rarely intra-abdominal alone. The spiral formed by the twist may extend well up into the abdomen from the sac toward the area of attachment to the transverse colon, thus involving progressively more and more of the omentum. When double, one twisted portion is found in the sac and the other may be found to be entirely independent and in the abdominal cavity.

In the variety associated with hernia, adhesions within the sac are very frequently found. It is possible however, for torsion to occur in the absence of peripheral adhesions.

Pathogenesis. The frequency with which hernia is found as a concomitant with omental torsion suggests an etiologic relationship. Usually the hernia is of long standing and reducible, and the omentum, continually pushing its way into the sac and then being replaced into the abdomen, is subjected to continued irritation over a long period of time. This results in a low-grade inflammation at the site, with thickening and the formation of a mass. Now, instead of a uniformly thinned-out border, the omentum at one point, has a knob hanging down from it. In the first instance,

(the normal condition) the apron-like spread over the intestine is maintained no matter how vigorous peristaltic movements may be. With a mass at any point on the free border, and with the omentum in constant motion as a result of peristalsis, there is a predisposition toward rolling, and after the first twist has occurred, some interference with the venous return occurs. This stasis, adding blood volume to the mass increases the tendency toward torsion. Thus a vicious cycle is established, the mass favoring a twist, and the twist increasing the size and weight of the mass. In confirmation of this explanation is the comparatively frequent occurrence of torsion associated with benign and neoplastic tumors, particularly along the edges of the omentum.

Torsion in those cases in which there are adhesions of the omentum to the periphery, to a hernial sac, or to any other point at one time the seat of an acute inflammatory lesion (appendix, tube, operative scar in uterus or abdominal wall, and others) is more readily understood. Under those circumstances with two comparatively fixed and oppositely placed points the intervening normal omental tissue, freely suspended, rotates like a "jumping rope" swinging in the hands of children. The rotary motion is imparted to it by the movements of the intestines, and here two twists occur, one at either end.

For the most infrequent variety of omentovolvulus encountered, the intra-abdominal type without adhesions or masses along the border, of which Rudolf collected twenty-three instances, Payr has offered a logical explanation. The veins of the omentum are larger and more tortuous than the arteries, and when they are compressed by a kink, they rapidly become engorged. The arteries in the attempt to propel the column of blood, form tense cords, about which the movements of the intestines twist the omentum. The twisting further embarrasses the circulation and this in turn predisposes to further rotation. The obstruction to the circulation results in inflammation and ultimately gangrene.

In this type as in the first type described, it is not uncommon to find a larger or smaller mass of omental tissue, at any stage in the inflammatory change from moderate edema and redness to massive gangrene hanging from a thinned-out, twisted pedicle.

Symptoms. The condition is more frequently encountered in males and in the fifth decade of life. In the history it is commonly noted that there has been a hernia of the inguinal variety of long standing. The sac may continually be empty, it may intermittently be filled with content, or the hernia may be of the irreducible variety.

A story of repeated attacks of sharp cramplike pains occurring suddenly and disappearing as suddenly after a short while, is occasionally elicited.

The acute torsion is frequently ushered in with a severe pain in the upper or the lower right quadrant of the abdomen. (If there is an associated hernia it is more likely to be the latter.) The

pain is increased with movement, and relieved by rest. Nausea and vomiting are not frequently complained of, but when they are, they often precede the pain. Varying degrees of tenderness and rigidity may be encountered, but these two symptoms are fairly constant in some measure. Careful examination reveals a mass, somewhat elongated, tender and usually movable. Occasionally it may be determined that the upper portion of this mass spreads out in a fan-shape to become lost in the region of the transverse colon. Usually tympany can be elicited on all sides of the mass. There is some leukocytosis, moderate fever, slight elevation of the pulse rate, and moderate toxic phenomena. Occasionally the proximity of the strangulating omental mass to the abdominal wall results in an inflammation by contiguity of the latter. This results in a deep bluish discoloration of the peritoneum and occasions a much more marked tenderness and rigidity. The degree of necrosis resulting from the interference with the circulation, determines the amount of peritoneal reaction and the severity of the toxic symptoms. As the condition progresses, abdominal distention becomes more prominent, and by careful percussion the presence of movable dullness in the flanks may be determined. Infection of the gangrenous mass may occur, and then the signs and symptoms of peritonitis overshadow the previously painted picture. Or the torsion may so shorten an adherent omentum as to first kink and then completely obstruct the transverse colon, in which event the predominating symptoms are those of intestinal obstruction.

The diagnosis is most commonly confused with two conditions. Where there is an associated hernia and the omental mass is situated low down in the abdomen, the diagnosis of appendicitis with abscess formation is often erroneously made. A history of many repeated attacks of pain is uncommon in acute appendicitis. In those instances where there have been previous attacks, the number is few. Appendicitis is distributed more equally between the two sexes, and it is more common between the ages of eight and forty. It bears no relationship to hernia, is ushered in with cramplike pains around the umbilicus, later localizing in the right lower quadrant of the abdomen, and the vomiting follows the onset of the pain rather than precedes it. Tenderness and rigidity are prominent symptoms and the localization is definitely over the region of the appendix. Most important, however, is the fact that the tumor mass in appendicitis rarely appears before two or three days after the onset and is fixed toward the right lateral border of the false pelvis, whereas in omentovolvulus the mass appears early, is movable, nearer the midline and because the ascending colon lies to its outer side, a tympanitic percussion note may be elicited external to the mass. These important differentiating points clearly define the two conditions.

In those instances where the omental mass is free and located

higher up in the abdomen, the condition is apt to be mistaken for acute cholecystitis.

Acute cholecystitis is much more common in females and the first attack of symptoms can frequently be linked with a definite pregnancy. Varying degrees of so-called "indigestion" are experienced by the patient for perhaps many years before an attack of acute pain. There is no relation to hernia. The pain during the crisis is in the right upper quadrant of the abdomen, is referred to the back and right shoulder frequently, and has a tendency toward paroxysms. Tenderness and rigidity below the right costal margin are prominent features and when the gall bladder reaches such a degree of distention as to be palpable as a mass, it is found to be continuous with the free border of the liver and not easily movable. The inability of the patient to take a full inspiration when the examining fingers are gently pushed up beneath the right costal margin in the region of the ninth and tenth ribs, is a constant differentiating sign. Icterus, when present, simplifies the diagnosis.

The differential diagnosis is not difficult. The great source of error lies not in the *inability* to distinguish omentovolvulus from other conditions. In diagnosing acute surgical diseases of the abdomen, omentovolvulus as a possibility, almost always is not *thought of*, and mainly for this reason so few cases are diagnosed preoperatively. The high degree of development which surgical craftsmanship has attained, is perhaps responsible for a tendency on the part of too many surgeons to be satisfied with the diagnosis of "acute abdomen" and to schedule the operation under no more exact title than exploratory laparotomy, when in a large number of these cases, more accurate diagnosis might be made by being more conscientious, painstaking and all-inclusive in reviewing the possibilities. Torsion of the omentum occurs with sufficient frequency to warrant consideration in the differential diagnosis of acute abdominal lesions, and given such consideration, the diagnosis will more often be made before operation.

Treatment. The treatment is always surgical and includes complete exploration of the omentum for more than one volvulus. It is not sufficient to merely untwist the inflamed portion. A radical removal of all of the omentum involved in the torsion must be accomplished to secure a cure. In this connection it is urged that the tissues be handled gently because of the possibility of embolism, (Perier) and that the pedicle be ligated in small sections, raw surfaces being properly cared for. Large mass ligature predisposes to further torsion and adhesions. The site of resection should be well above the level of obliterated circulation. The abdomen should then be inspected for accompanying inflammatory lesions, with which omentovolvulus is so frequently associated. If any such lesion be found, it should be eradicated by appropriate treatment. It must be remembered that the omentum, while very easily

removed from the body without immediate danger to life, is nevertheless a very important structure, and as such, worthy of as conservative surgery as is consistent with the lesion. Its gliding and sliding movements determine peritoneal fluid currents which are related to absorption in inflammatory conditions. These movements contribute a buffer activity which is unparalleled in any other tissue. Thus it has a tendency to close up apertures in the abdominal wall, (stab wounds) or in the abdominal viscera (perforated ulcers). It helps circumscribe and limit infection by wrapping itself around a suppurative appendix or an inflammed gall bladder. The experiments of E. de Rienzi and Boeri demonstrated that in a few hours the omentum encapsulated an organ deprived of its blood supply. The author, in an experimental study on peritoneal adhesions found that three hours after the omentum of a cat (which normally always envelops the intestines) is rolled up and tucked under the liver, leaving 5 cc. of tincture of iodin in the abdominal cavity, it completely unrolls and wraps itself entirely around the intestines as though to protect them from the injurious effects of the iodin.

These movements of the omentum are influenced by respiration, gravity, peristaltic intestinal movements, changes in intra-abdominal pressure, torsion action of the arterial pulse in the bloodvessels of the omentum. They are also governed by its peculiarly smooth and slippery surface, and a singular property probably allied to general chemotactic phenomena and perhaps influenced by the large number of macrophages which normally inhabit it, and by the large number of leukocytes with which it can be flooded at short notice.

In the omentum are found a large proportion of the histiocytes of the reticuloendothelial system of Aschoff and others. To these cells, besides the ordinary phagocytic activities, have been ascribed such important functions as participation in destruction of erythrocytes and platelets, formation of bile pigment, formation of antibodies, storage of lipoids and iron, metabolism of phosphorus, and others. It must be remembered, therefore, that excision of large portions of the omentum accomplishes more than merely the removal of a large quantity of fat.

The omentum acts as one of the great fat depots of the body and in that sense is a valuable storehouse for energy. It also, because of its bloodvessels and lymphatics, is very active in the absorption of liquid and particulate matter from the peritoneal cavity. Because of its rich vascularity and the loose network of veins not supported by enveloping tissues which might interfere with ready and great dilitation it supplies an important adjunct to the pressure-regulatory mechanism of the circulation. For the same reason, it has been able, through the medium of adhesions, to furnish sufficient accessory blood supply to organs deprived of their circulation to keep them viable.

All of these facts emphasize the value of the omentum to the body, and the importance of conservation in the treatment of lesions of the omentum.

Case Report. CASE I.—J. A., male, aged fifty-eight years, married, was admitted to the Brownsville and East New York Hospital, April 3, 1925, complaining of pain in the right upper quadrant of the abdomen. The family history was negative. He had always enjoyed good health and had never been troubled by any gastrointestinal disturbances.

Present Illness. On the day before admission the patient was suddenly seized with severe pains in the right upper quadrant. There was no nausea, vomiting or belching. The pain however, grew progressively worse, was not relieved by ice, or a narcotic. Physical examination revealed a well-built, well-nourished man with good color. There was a corneal opacity in the right eye due to old injury. Respiratory movements were rapid, shallow and chiefly costal, but pulmonary resonance and breath sounds were normal. The apex beat was in the fifth interspace, 4 inches from midsternal line, regular, no thrills palpable, no cardiac enlargement noted by percussion, no murmurs audible, sounds clear. The abdomen was ovoid, immobile, distended, markedly rigid especially in the right upper quadrant and very tender, particularly so in the right upper quadrant. There was pressure-release tenderness all over the abdomen always referred toward the right upper quadrant in the neighborhood of the gall bladder. There was a mass palpable, the upper border of which disappeared under the right costal arch, and it extended down almost to the level of the umbilicus. It was very tender and attempts to move it were interfered with by the distention and rigidity. No dullness was elicited in the flanks. The extremities and reflexes were normal. Temperature was, 103.2; pulse, 116; respirations, 32. The urine showed a specific gravity of 1019, acid reaction, was negative for albumin and glucose, contained few hyaline and granular casts, an occasional leukocyte, few bladder cells and urate crystals. The hemoglobin was 90 per cent; leukocytes, 12,400; polymorphonuclears, 77 per cent; transitionals, 1 per cent; large lymphocytes, 4 per cent; small lymphocytes, 18 per cent. With a preoperative diagnosis of acute cholecystitis, a high right-rectus incision was made. There was considerable free fluid in the abdomen, the peritoneal surface of the right upper portion of the abdominal wall was purplish in color and closely approximated to it was the palpable mass which instead of gall bladder was a large portion of the omentum rolled into a mass by many twists of its proximal portion. The mass was strangulated, the circulation being completely interfered with. The gall bladder and liver were normal. The appendix was deeply buried in the iliac fossa by old adhesions. The gangrenous omentum

was excised after ligation of the pedicle and the appendix removed and the abdomen closed. Convalescence was uneventful and rapid.

Case II.—I. M., female, aged forty-four years, married, was admitted to Brownsville and East New York Hospital, January 19, 1926, complaining of pain in the right upper quadrant of abdomen of five days' duration. The family history and previous personal history were entirely irrelevant to the present illness. She never had any gastrointestinal disturbances. Present illness began five days before admission with sharp pain in the epigastrium, radiating to the back between the "shoulder blades." The pain was accompanied by vomiting and not relieved by it. It gradually shifted to the right side of the abdomen in the upper half and there remained constant. There was no constipation, belching nor heart burn. Pain was not relieved by narcotics. Physical examination revealed a rather obese patient, of poor color, with pupils equal, regular, and reacting readily to light and accommodation. The teeth were in good condition. There was normal pulmonary resonance and breath sounds. The heart sounds were of fair quality, regular; there were no murmurs, thrills or cardiac enlargement. The abdomen was protuberant, the liver and spleen not palpable, but there was a suggestion of a mass in the midclavicular line extending from the costal margin almost down to the level of the umbilicus, which was tender, dull on percussion, about 3 cm. wide, not readily movable. Some rigidity was present in the upper right quadrant, and pressure-release tenderness on the left side of the abdomen was reflected toward the mass. No ascites was discovered. Other findings were: Temperature, 101.2; pulse, 90; respirations, 24. The urine showed a specific gravity of 1025, acid reaction, clear, negative for albumin, sugar and bile, no casts, few bladder cells. The leukocyte count, was 11,200; polymorphonuclear cells, 78 per cent; eosinophiles, 2 per cent; small lymphocytes, 18 per cent; large lymphocytes, 2 per cent. With a preoperative diagnosis of acute cholecystitis, the abdomen was opened by a high right-rectus incision. There was some serosanguinous fluid, the gall bladder was normal but lying in front of and below it was a gangrenous mass of omentum hanging from the transverse colon by a narrow twisted pedicle which had made eight complete twists. The mass was carefully excised, the appendix, macroscopically normal, was removed, and the abdomen closed without drainage. Convalescence was uneventful and rapid.

Summary. Here were two cases of omentovolvulus of the variety without co-existing hernia, in which the omentum alone was involved, without adhesions to neighboring viscera. The mass was palpable abdominally, presented in the right upper quadrant in the region of the gall bladder, and was accompanied by the signs of obstruc-

tion to its circulation, namely, serous peritoneal reaction with temperature and pulse rise, localized tenderness and rigidity, and both cases were erroneously diagnosed as cholecystitis.

Retrospection confirms the feeling that the consideration of omentovolvulus as a possibility in the diagnosis of acute abdominal lesions will lead to its more frequent preoperative recognition.

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SYMPTOMS ASSOCIATED WITH IODIN DEFICIENCY IN SIMPLE GOITER.

A Clinical Study.

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The conception that iodin deficiency is the cause of simple goiter has found widespread acceptance. It has been observed clinically and demonstrated experimentally that when the iodin content of the thyroid gland drops below 1 per cent, hypertrophy and hyperplasia begin.[1,2,3,4] If the deficiency persists for a sufficient length of time, or is sufficiently intense, the gland appreciably increases in size and a simple goiter results. The degree of thyroid hyperplasia apparently depends upon at least two variables, time and intensity, and is inversely proportional to the iodine content of the thyroid gland.[3]

The first evidence of the development of a simple goiter is a decrease in the iodin content of the thyroid gland.[3] As this is not

a practical clinical criterion the increase in the size of the gland itself is usually the first indication of a simple goiter. In an otherwise normal thyroid this would make a wide zone of safety. The hypertrophy may not become obvious until an iodin deficiency has been present for a considerable length of time.

The deficiency of iodin in the thyroid may be brought about in two different ways: By a decreased intake of iodin or by an increased demand for iodin by the body. In other words, a simple goiter may result either from a relative or an absolute iodin deficiency.[5]

Furthermore it is a long-standing clinical observation that enlargement of the thyroid is more likely to occur in females than in males and is more frequent at certain periods of life: fetal life, puberty, pregnancy, lactation and menopause. The explanation for the difference in sex and the susceptibility at certain ages is largely wanting. It is conceivable that the increase in heat production which has been demonstrated during pregnancy[6,7,8,9] and to a lesser extent during menstruation[9] leads to an absolute iodin deficiency.

During the past three years, the Endocrine Clinic at the New Haven Hospital and Dispensary has offered an opportunity for studying a comparatively large group of patients with thyroid disease, in which all the clinical varieties were represented. Among these patients there were a number of schoolchildren who showed various degrees of thyroid enlargement. In this group were patients who presented, in addition to thyroid enlargement, certain general constitutional symptoms; and some who presented the same general symptoms but in whom the thyroid was not enlarged or at least could not be palpated. A study of these cases was undertaken to determine: (1) If there were any more than a casual relation between the symptoms observed and the thyroid enlargement in those cases in which a goiter could be detected clinically; (2) the subsequent course when treated symptomatically without iodin; (3) and later the response to iodin therapy. The basal metabolic rate was determined when possible and other laboratory and diagnostic procedures were carried out when indicated to assist in the diagnosis.

The patients varied in age from seven to eighteen years. There were nine girls and five boys. The history and physical examination of these cases are so similar that only four will be presented in detail to show the slight variation due to age, sex and so on.

Case Reports. CASE NO. 41037.—A schoolgirl, aged eleven years; Irish; weight, 66 pounds; height, 5 feet 3 inches, on October 20, 1924, was brought to the Dispensary because of attacks of cardiac palpitation of about four weeks' duration. The first attack was experienced in the schoolroom. The patient noticed that her heart was beating very forcefully and rapidly. This frightened her and she asked to go home. A physician who was summoned to her home found nothing except a rapid heart action. There were no associated symptoms such as shortness of breath or change

of color. She felt better after a few days but complained of frequent attacks of palpitation and some precordial pain following usual exercise.

She had been restless and irritable since school began in the fall, finding it difficult to study. In consequence she dropped from the top to the middle of her class. More recently she had displayed great fear of the dark. Insomnia and anorexia developed. She had never menstruated. Family history and past history unimportant.

She appeared well developed and well nourished, unapproachable and backward and somewhat nervous. The face was flushed. The tonsils were large but clean. There was slight but definite, symmetrical enlargement of the thyroid; marked pulsations over the large vessels of the neck; pulsation with bruit at upper poles of the thyroid; no thrill. There was considerable lid lag with some widening of the palpebral fissure; fine tremor of the fingers. No substernal dullness. Over the precordium were visible pulsations, most marked in region of the nipple and a forcible, thrusting impulse. The heart was not enlarged and no murmurs were heard; marked sinus arrhythmia was present. Pulse regular; rate 135 per minute, after twenty minutes' rest. Chest was clear; abdomen, negative. Deep reflexes hyperactive.

Impression: In spite of her age the patient presented a condition suggestive of early exophthalmic goiter. It was impossible to determine the basal metabolism because of lack of coöperation. She did not keep appointments and was not seen again until January 15, 1925, when her symptoms seemed to be intensified. The thyroid was freely palpable and more vascular. It was very difficult to examine her because of restlessness and muscular twitching. At this time she was given Lugol's solution, 2 drops per day.

On February 10, 1925, she seemed greatly improved; looked rested, had been sleeping well, her tremor was less marked, and she was less nervous. Palpitation had disappeared after the second day of treatment. Weight 67¾ pounds.

On February 24, no palpitation, no tremor or muscular twitching, thyroid was smaller, soft and less vascular. Pulse 100 per minute.

March 24. General condition much improved. Pulse 100 per minute.

May 5. General condition unchanged but pulse only 78 per minute.

May 19. Pulse 76; weight 70 pounds. Lugol's solution discontinued.

August 25. Weight, 72 pounds; pulse, 76. Patient had been well. None of the symptoms persisted and the thyroid was just palpable.

January 26, 1926. Examination at that time showed a perfectly normal child, except for a slightly palpable thyroid. She was again leading her class in school. She had received 3 drams of hydriodic acid per day for two weeks and repeated at two month intervals since the Lugol solution was discontinued.

Case No. 8672.—A boy, aged seven years, was first seen in the Pediatric Clinic on June 27, 1922, because of acute pharyngitis. The physical examination was reported negative except for the acute infection and the fact that he was slightly underweight. He was not seen again until December 2, 1925, when his mother brought him to the Clinic because of anorexia and failure to gain weight. He had also been restless and irritable; his sleep was disturbed by bad dreams and he tired easily during the day. His work in school had been poor all the year. For the last two or three weeks he had been kept from school by his present illness. He had always been considered a delicate child, slightly underweight but had been sick but very little. Family history unimportant.

He appeared small for his age, pale and delicate, of good intelligence and interested in everything about him, but continually restless. His skin was

soft and warm, his palms moist. There was definite widening of the palpebral fissures but no lid lag; marked throbbing of vessels in neck. The thyroid was palpable. Fine tremor of fingers. The sudden contracture of the muscles of the arms and the turning of the head was a conspicuous feature; at first this suggested chorea, but in no sense was it typical of the purposeless movements seen in patients with chorea. Pulse, regular; rate 110 per minute at rest. Blood pressure: Systolic, 118; diastolic, 68. Blood Wassermann, negative. Urine, negative. Red blood cells, 3,900,000; hemoglobin, 75. December 21, 1925, Basal metabolism, − 6. Therapy: Syrup hydriodic acid, 1 dram per day.

January 16, 1926. His condition was greatly improved; he looked rested, slept well and had a good appetite. The fine tremor of his fingers had disappeared and there were no visible pulsations in his neck. Pulse 84 per minute.

February 2, 1926. Examination showed a normal boy except for slight pallor and small size. He was back in school and doing well with his work. Urine, normal. Red blood cells, 4,100,000; hemoglobin 80 per cent.

Case No. 35327.—A girl, aged thirteen years, referred to the New Haven Hospital on December 3, 1924, for tonsillectomy. At that time an enlargment of the thyroid was noted and she was referred to the Endocrine Clinic. She had lived in Maine until about two years ago. The swelling in her neck was first noticed by her mother when she was nine years old. She had been in the best of health until about seven or eight months ago when she became nervous and irritable. She had been forced to stay out of school frequently during the year, but her mother had ascribed her symptoms to the onset of menstruation, which had begun about nine months earlier and had been entirely normal.

Examination showed a tall and slightly delicate girl, weight, 112 pounds; height, 5 feet 5 inches; whose facial expression gave the examiner the impression that she had had very little sleep recently and was partly exhausted. The general physical examination was negative save for moderate pulsation of the neck vessels; moderate symmetrical enlargement of the thyroid; a bruit over the right upper pole of the gland; a fine tremor of the fingers, and a resting pulse rate of 120. Eye signs were lacking. Blood and urine normal.

June 24, 1925. High caloric diet, mild sedatives and rest periods had resulted in no improvement. Weight, 113 pounds. Pulse, 100 per minute. Basal metabolism, − 4.3. She was ordered to continue the dietary and rest regime, and in addition to take syrup of hydriodic acid, 1 dram three times a day.

July 8, she was greatly improved; her appetite had improved; she slept well and seemed rested and less nervous. Pulse, 90 per minute.

December 15. Examination at this time showed nothing abnormal except a moderately enlarged thyroid. Pulse, 84; weight, 115 pounds.

Case No. 42827.—On May 22, 1925, a girl, aged thirteen years, was referred to the Clinic by a public-school nurse because of a swelling in the neck and palpitation of the heart of two months' duration. The palpitation occurred at first only after exercise but more recently had appeared even when she was lying down or sitting in the classroom. She appeared slightly underweight, with an anxious expression on her face and was quite restless. Her skin was soft and of good color, her palms were moist. There was a moderate diffuse enlargement of the thyroid; with noticeable pulsations in the neck and a bruit but no thrill at the upper poles. There were no eye signs. There was a forceful, visible impulse over the entire pre-

cordium; the heart was normal in size without murmurs. Blood pressure: Systolic, 110; diastolic, 60. Pulse, 98 per minute. The deep reflexes were hyperactive and there was a fine tremor of the hands. Basal metabolism, − 8; weight, 103 pounds. These signs and symptoms suggested a case of early exophthalmic goiter. Therapy: Syrup of hydriodic acid, 1 dram three times a day.

June 23. She looked and felt much better. The palpitation had ceased; the pulsations in the neck and over the heart were less marked. The thyroid was softer and both bruit and thrill had disappeared. No fine tremor. Pulse 80 per minute.

December 12, having continued the same therapy, she presented nothing abnormal except a freely palpable, soft, symmetrical enlargement of the thyroid. Pulse, 78; weight, 106 pounds.

Comment. There is a notable similarity between these cases. The symptoms are nervousness, increased irritability, palpitation and associated symptoms such as poor appetite, disturbed sleep, fatigue, and inability to gain weight. The physical findings are enlargement of the thyroid, in most instances, with evidence of increased vascular supply; tachycardia, fine tremor of the fingers but never more than suggestive signs of exophthalmos. These symptoms and findings strongly suggest hyperthyroidism or early exophthalmic goiter, a diagnosis which was made in several instances on the first visit. However, when the basal metabolic rate could be determined satisfactorily, it was found to be within normal limits and usually at the lower zone of normal.

The symptoms and signs were little affected by rest, diet and general hygienic measures, but responded rapidly and favorably to iodin. The improvement under iodin therapy was similar to that observed in exophthalmic goiter though less spectacular, and was more durable, persisting for over a year in several instances. The iodin was given in the form of Lugol's solution, 2 drops per day, or syrup of hydriodic acid, 3 drams per day for a period of two weeks and repeated at two or three months intervals thereafter. At the end of the first two weeks all the patients showed marked improvement or complete relief of symptoms. However, in 2 or 3 cases the symptoms did not completely subside for over a month. If the thyroid had been palpable before treatment it invariably became soft and smaller. The patients, in whom the thyroid was enlarged exhibit at this time the classical findings of colloid or resting goiter, in no instance has there been a recurrence of symptoms.

From the latest textbooks and the more recent articles on this subject, one is given the impression that simple goiter is primarily a disease of the thryoid gland and that it may be important clinically either by reason of the size of the gland or by causing symptoms that have no relation to size, but depend upon anatomic position. The only constitutional symptom that is commonly mentioned is occasional palpitation.

Although the cases reported here present evidence of some functional disturbance of the thyroid, they cannot be fitted easily into the accepted classification. The time of onset, the normal or slightly lowered basal metabolism and the durable response to iodin therapy are not characteristic of exophthalmic goiter or the other ordinary types of hyperthyroidism.

It is not intended to present this symptom complex as one never previously observed or described. It is probable that it would be encountered more frequently in areas where the incidence of simple goiter is high. There are in the literature numerous descriptions of similar cases which are classified under various names.

It was pointed out above that an iodin deficiency of the thyroid probably exists for a considerable time in most instances before objective evidences of thyroid hypertrophy appear. This deficiency may develop so gradually or intermittently, in most cases, that no symptoms other than the thyroid hypertrophy ever manifest themselves. In a certain number of instances the deficiency may develop so rapidly that it results in associated general constitutional symptoms by causing not only an iodin deficiency of the thyroid but also a nutritional disturbance of the tissues of the body, of which the goiter is but a symptom.

At present we have no knowledge of the role of iodin as such in cellular nutrition except the part played when it enters the molecule of the thyroid hormone, thyroxin. However, its effect in the prevention and treatment of simple goiter is well established.[5] It is also known to be present in small but constant amounts, in all the tissues of the normal body and in much larger amounts (average 2 mg. per gram)[10,11,12,13] in the thyroid gland, which is peculiar in this respect. It was shown by Marine in 1916, and by Loeb in 1920, that thyroid grafts can be made to undergo hyperplasia or involution at will by the production of iodin deficiency or iodin excess in the host. Hudson's work[16] suggests that the iodin level of the blood stream may be controlled by the thyroid in a manner analogous to that in which the blood-sugar level is controlled by insulin. Marine[3] has shown that hypertrophy of the thyroid is closely related to the physiologic iodin deficiency of that gland. This hypertrophy he considers a response to overwork.

The cases herein described would seem to fall into the classification of simple goiter, but are unusual in that they show certain general symptoms in addition to the goiter. Whether the disturbance is due to an excess or a deficiency of some substance, we have no exact knowledge, but that it is closely related to thyroid hypertrophy, seems quite evident. It is reasonably certain that the symptoms cannot be accounted for by a change in thyroxin production because there is no change in the heat production. The subsidence of the symptoms under iodin therapy suggests that the disturbance is closely related to the iodine deficiency of the thyroid.

Summary. An unusual symptom complex has been observed in 14 patients. Four typical case reports are given. The patients varied in age from seven to eighteen years. All presented symptoms suggestive of hyperthyroidism, usually attended by definite enlargement of the thyroid gland. The basal metabolism, on the other hand, was normal. Symptoms and signs were in every case rapidly and permanently relieved by the administration of iodin.

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CONSTITUTIONAL AND HEREDITARY TRAITS IN DIABETICS.

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Today health is defined as "the capacity of an organism for adequate response to influences in its surroundings,"* and disease

* Barker, L. F.: Comments on Health and Life, Ann. Clin. Med., January, 1926, **4**, 525.

is defined as "an expression of the reaction between a complex set of external agents and an equally complex organism, striving to survive."*

An individual is destined to have good or bad health, inasmuch as he cannot change the substance of which he is made, and only to a limited extent alter the external conditions which surround him. Thus are we forced to admit definite limitations to the conquering of disease and health as well. The individual does best, whose protective reactions are so developed that he instinctively avoids strain or stress, and lives within his innate physical capacities.

If the science of endocrinology continues its advance we shall sooner or later be forced to a readjustment of some of our views. We will have made a great advance when we know how and to what extent internal secretions protect the body against the effects of bacterial invasion. It is a tragedy indeed that hyperactivity of one's posterior pituitary before puberty makes him extremely tall and when it occurs after full height is attained, the skeletal parts grow broad and coarse and abnormally heavy. It is a tragedy that oöphorectomy alters the physical and psychical components of a previously normal woman; and that overfunctioning or diseased adrenals may make a man hairy as an ape. A diseased thymus producing status lymphaticus, gives man the integument of a woman, and such a man may be killed by a whiff of chloroform. The individual with status lymphaticus is altered both physically and psychically. Careful observers have noted that he, more frequently than any other type, is the victim of suicide. It is the height of tragedy that a tumor of the pineal body, in certain ways, can make a child of five years masculinely and psychically mature within six months.

To what extent endocrine dysfunction determines the physical and psychic reactions of man to his surroundings may not at this time be conjectured with too much certainty, although all of us know how thyroxin, adrenalin and pituitrin alter mental and physical reactions.

At least it is a step forward, that we have come to the place where we may now begin to evaluate certain facts. It is also quite apparent that there is a constant tendency on the part of Nature to balance the internal secretions, and that on the whole this tendency to balance is greater than the tendency to imbalance. Enough is known of pituitary, thyroid, thymus, ovarian and testicular dysfunction, to warrant the belief that good equilibrium determines a healthy existence for the individual.

All this opens a new vista, creates new interests and affords new opportunities to the physician. Many long-established clinical syndromes may now be approached by a new avenue of thought;

* Draper, George: Human Constitution, Saunders Company, 1924.

if not so much for the purpose of renaming or reclassifying old diseases, then for shedding new light on old problems.

With this viewpoint in mind, I wish to discuss certain clinical findings in diabetic patients. It is not sufficient to say that diabetes is a disease involving the pancreas, in which insulin production has failed because of an inherent weakness of that organ or because of a chemical or bacterial injury. There are evidences in the diabetic which suggest that we are dealing with a type of patient who is marked with certain constitutional water marks, and there are other evidences which suggest that these constitutional traits are intimately associated with the endocrines. With the advent of insulin, we have been forced to a revaluation of values in our knowledge of diabetes, and out of this, much good has come.

Since 1923, we have been gathering data on diabetic patients. Our series now comprises more than 350 cases and it has seemed worth correlating some of these observations.

Nutritional History. We recorded the patients' weight at four periods: (1) At the age of twenty-one years, the time of maturity; (2) the maximum weight and the age at which it was attained; (3) the time when weight began to diminish; (4) at the beginning of treatment. In Group A, 100 cases, our findings show that at twenty-one years the weight was normal. Between the age of twenty-one years and the time when diabetes was discovered, the average increase in weight for the series was 59.5 pounds per person. Ten of this group did not become obese, but they averaged 7.6 pounds above average weight for their age and height. In Group B, 100 cases, the average weight per patient was 185 pounds. For the entire series of 350 cases our records show that 90 per cent were obese.

Dietetic Habits. In the light of preconceived ideas, an inquiry into the dietetic habits of these patients, was not as satisfactory as it might have been. Only 20 per cent gave a definite history of overeating. Certainly there are many gourmands who do not develop diabetes. Also there are large eaters who apparently do not metabolize their food, and do not become obese and therefore do not strain their metabolism.

And there is a distinct group of obese persons whose metabolism is run on an economical basis. They are small eaters habitually; and they and their families aver that while they are the fattest member of their family, they are likewise the smallest eaters. I have had the experience of keeping such obese patients on a hospital controlled caloric diet, allowing 20 calories per kilo body weight and permitting walks of 2 to 4 miles daily, without loss of body weight, and at the end of a three-week period to have counted the reduction treatment a failure.

It is, of course, true that the majority of diabetics, as well as most nondiabetics, overeat. It is not an uncommon experience in

nondiabetic patients after restricting the diet to half of their former intake, that weeks or even months may go by without appreciable effect on body weight. Whether it is permissible to draw conclusions from statistical data, that increasing sugar consumption throughout the land is a responsible factor in the increasing numbers of reported diabetics, is not certain. The history in some of our diabetics indicated clearly that obesity came on suddenly and without discoverable cause on the part of the patient; and that it was independent of diet, habit or occupation, suggesting that an unknown change had suddenly taken place in their metabolism.

Height and Weight. Is there anything characteristic in the type and body conformation of the diabetic? In a group of 190 diabetics, our observations showed that 111 were shorter than the average normal, 42 were of average height, and 37 were above average height. As a class, compared with nondiabetic groups, diabetics are distinctly shorter in stature than nondiabetics. It was previously stated that 90 per cent of diabetics are obese at middle life. These two observations pertaining to shorter stature and greater weight lead to a noteworthy third observation. I have been repeatedly impressed with the fact that many diabetics who have the outward appearance of sthenic or hypersthenic type of individuals are actually not of that type. In reality they have slender framework and small skeletal features, hidden by pads and rolls of fat, which give them the outward appearance of being large. I have noticed this particularly in patients who having weighed 200 pounds had reduced to a weight of 100 pounds. At the latter weight it was apparent that they were much nearer normal. The head, the torso and extremities all seemed in normal proportion. What previously looked like an abnormal hand tapering to the tips and sometimes called the pituitary type of hand, was really a normal hand covered with pads of fat. The strikingly slender ankle of the fat woman was really the normal ankle of a small person. The wrist, forearm and arm were likewise normal. The thorax seemed normal in size; this type of individual presents no skeletal disproportion. The abnormality consists of excessive fat deposits.

Complexion. In a group of 182 diabetics, 140 were light complexioned and 42 were dark. Light complexion is very characteristic, and is an element in the composite picture of the typical case of diabetes. To what extent, and which endocrine functions more than another, determines the degree of pigmentation, is not certain. The coloration in adrenal disease is well known. And what is more striking than the complete change of color in the skin, within two or three days after a thyroidectomy?

Hirsuties and Skin. The typical diabetic is light complexioned, has a scant covering of hair over the body, and the skin is abnormally smooth. Late in the disease when the fat has been used up and subcutaneous tissue is atrophied, the skin is very transparent and can be moved over the underlying tissue *en masse*. This is par-

ticularly noticeable over the thorax. In those who have reached a state of undernourishment, especially the light complexioned, the hair of the scalp will be found of very fine texture, faded and mottled in coloring, often giving the appearance of hair which had been dyed red and partly washed out. Its fine texture is very striking. This in part is due to atrophy from undernourishment. Our observations indicate that diabetics constitute a group in which light complexion is the dominant color, and they also indicate an existing relationship to the endocrine functions which have to do with skin coloration.

The Thyroid Gland. The thyroid gland is frequently involved in diabetes. Glycosuria is commonly found in hyperthyroidism. The glucose tolerance test in patients with hyperthyroidism gives a nondiabetic blood-sugar curve. In 366 cases of diabetes we found abnormally large thyroids in 57. These thyroid glands varied from moderately enlarged glands to extremely large and disfiguring goiters. They were of the simple colloid and adenomatous type. In 2 patients thyroidectomy was performed.

Lesions of the Skin. In the last 100 cases of our series, we found papillomas over the neck, thorax and abdomen in 28; small angiomas over the thorax and abdomen, varying in number from a few to a hundred in 27 cases; xanthomatous plaques in 4; and diffuse brown pigmentation in 4. These findings occur with sufficient frequency to suggest a relationship between the underlying cause of the disease and the integument of the patient. In no other group of patients do we find these lesions as often as in diabetes.

Hereditary Tendency. In 350 cases, we obtained a history of diabetes involving more than one member of the family, 68 times. In these 68 families there were 85 diabetics. (See Chart I.) At times this family tendency is striking. I am now treating a patient whose father and mother were diabetic, two sisters with diabetes, two diabetic brothers, a diabetic woman who has one daughter with diabetes and another who is a classical case of renal glycosuria, also a woman whose uncle, brother and son have diabetes. I have under my care a man and his wife who are diabetic, but I do not consider their conjugal diabetes of more significance than two other diabetic patients of mine, who are partners in business.

Functional Capacity of the Pancreas. Up to this point we have established for the diabetic patients of this series, the facts that the majority were of shorter stature than the average, and that at maturity all were of average normal body weight, and at middle life they became markedly obese, averaging 59.5 pounds above normal. May we infer from this, that a person of a certain size is by nature endowed with a pancreas capable of functioning for him as he is at maturity when he is at high physical efficiency? And may we also infer that unless such a pancreas is unusually efficient, it may fail to meet the functional requirement of the individual after he has increased 59.5 pounds in weight?

The increased weight of the diabetic consists mainly in an increased fat deposit. Fat metabolism as we conceive it today, concerns the pancreas more than any other organ. The majority of our patients developed diabetes between the ages of forty and sixty years. (See Chart II.) This in turn also implies that pancreatic function in these patients withstood the strain to which it was exposed for approximately twenty-five years.

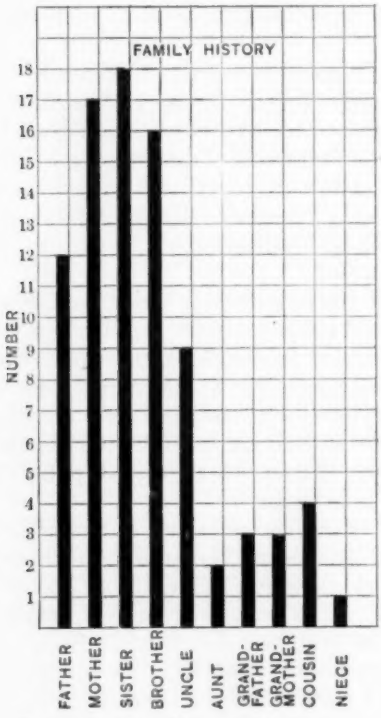

CHART I.—Hereditary tendency in diabetes.

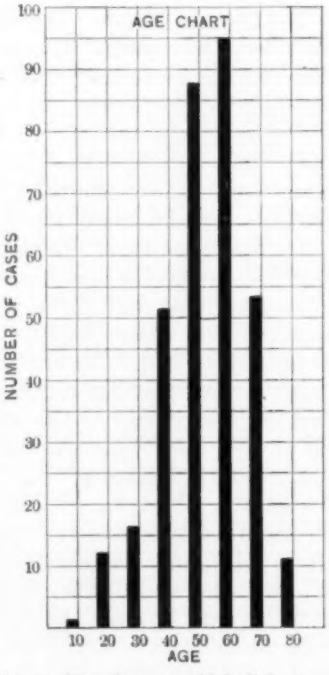

CHART II.—Ages at which diabetes developed.

Summary and Conclusions. We have linked together some findings in diabetic patients which occur with sufficient frequency to give them clinical significance. If it cannot be said that an individual having these stigmata is predestined to become diabetic, these observations do justify us in saying that in diabetes they occur with striking coincidence. We look upon the stature, obesity, coloring, lesions of the skin, endocrine disturbances, family history of diabetes and the other findings to which we have referred as indicating constitutional disturbances, which make an individual diabetic. They seem intimately concerned in the cause and the effect of the disease. An individual who presents these findings, is the kind of an individual who develops diabetes.

STUDIES ON THE QUANTITATIVE ESTIMATION OF THE TOTAL PROTEIN CONTENT IN CEREBROSPINAL FLUID.

With Description of a New Method.

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and

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The need for a simple practical method of determining the total protein content of cerebrospinal fluid is recognized by everyone who examines many spinal-fluid specimens.

The various rough qualitative methods of globulin determinations are universally unsatisfactory. Opinions differ with any of the qualitative methods as to the dividing line between pathologic increase and a normal fluid, except where the globulin is greatly in excess.

For a number of years one of us, (G. A. Y.) has been using a gross total protein precipitation determination of cerebrospinal fluid as suggested by Sidney Mann in Mott's laboratory in London. This method consists of mixing three parts of 95 per cent ethyl alcohol and one part of cerebrospinal fluid, acidulating slightly with acetic acid and boiling. The resulting flocculation of protein was compared with normal in terms of 1 +, 2 +, 3 +, 4 +. The increase varies from slight turbidity to heavy flocculation. In pathologic fluids a heavy flocculent precipitate occurs. This gave one of us (G. A. Y.) the idea of measuring the amount of precipitate. This problem was solved by using a capillary-tipped vaccine tube, which tip is calibrated from 0.01 to 0.05 cc. Centrifuging at high speed throws down the precipitate, so that it can be read quantitatively and compared with our known normal.

For the last four years we have used this method exclusively in approximately 600 determinations in private practice. Hundreds of determinations have been made by other laboratories elsewhere in the city and at the University of Nebraska College of Medicine. The method has given complete satisfaction to those who have used it.

Method. The method is as follows: Two cubic centimeters of cerebrospinal fluid are measured into an ordinary graduated centrifuge tube. Ethyl alcohol, 95 per cent, is added up to 8 cc. (1 cc. of fluid and up to 4 cc. with alcohol may be used and gives a better reading where the protein content is greatly increased). The

contents are then acidulated with a drop of 10 per cent acetic acid or *just a trace* of glacial acetic acid. The contents are then heated carefully to boiling over a Bunsen burner. The protein immediately flocculates. The contents of the centrifuge tube are transferred to a vaccine tube with the capillary tip graduated in 0.01, 0.02, 0.03, 0.04, and 0.05 cc. and centrifuged until the precipitate is all thrown down into the capillary tip. Some of the precipitate may collect on the sides, then the supernatant solution is stirred with a glass rod and the contents centrifuged again.

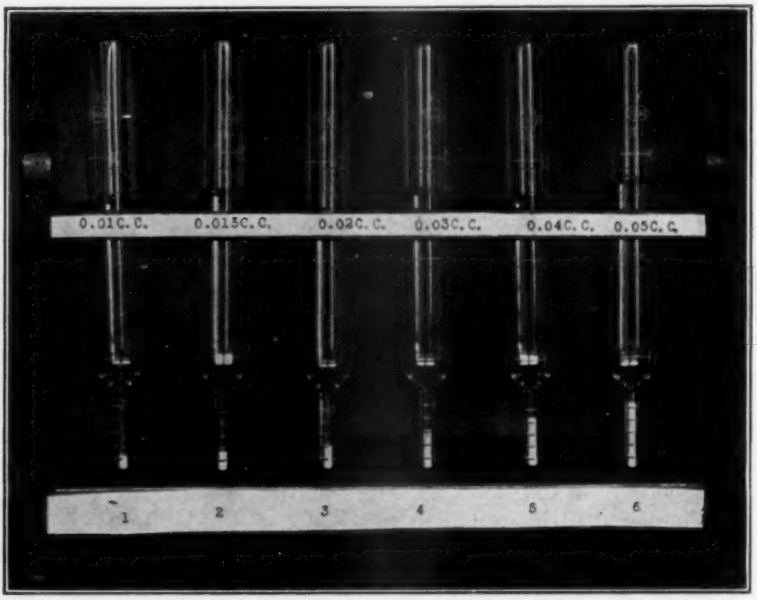

FIG. 1.—Showing varying amounts to total protein precipitate in cerebrospinal fluid as seen in the vaccine tubes after centrifuging. Determinations made by using 2 cc. of cerebrospinal fluid.

1. 0.01 cc. or 50 mg. per 100 cc. Normal
2. 0.015 cc. or 75 mg. per 100 cc. High normal
3. 0.02 cc. or 100 mg. per 100 cc.
4. 0.03 cc. or 150 mg. per 100 cc.
5. 0.04 cc. or 200 mg. per 100 cc.
6. 0.05 cc. or 250 mg. per 100 cc.

The amount of total protein normally present in 2 cc. of cerebrospinal fluid as determined by this method is from 0.005 to 0.015 cc. or from 25 to 75 mg. per 100 cc. We have been using 2 cc. of cerebrospinal fluid because this amount gives a larger quantity of precipitate and a better volumetric reading unless the protein content is greatly increased; then 1 cc. is used. The method is simple, practical and clinically accurate. The determination can usually be completed within three minutes when centrifuged at the rate of

3000 revolutions per minute. The reagents are simple and no elaborate apparatus or preparation of standards are required. The vaccine tubes can be procured from any supply house making laboratory glassware. The precipitate is readily removed from the capillary tip by using a capillary tip pipette with a rubber bulb from a medicine dropper fastened to the large end.

Results. Table I presents the pathologic specimens of cerebrospinal fluid, in which an excess of total protein content was found by this method. These are only specimens in which the total protein content was increased and are taken from about 600 cases.

TABLE I.—TABULATION OF PATHOLOGIC TOTAL PROTEIN DETERMINATIONS.

	Number of cases.	High mg. per 100 cc.	Low mg. per 100 cc.	Average mg. per 100 cc.
1. Neurosyphilis				
(*a*) Paresis and taboparesis	57	500	87	200
(*b*) Tabes dorsalis	21	175	75	100
(*c*) Cerebrospinal syphilis (meningovascular, gummatous types)	38	275	75	125
2. Cerebral arteriosclerosis (thrombotic, aphasic, hemiplegic types)	7	200	75	100
3. Epidemic encephalitis (acute)	17	200	75	125
4. Acute polyneuritis	5	125	87	100
(*a*) Central neuritis or neuronitis	2	500	400	450
5. Brain and spinal-cord tumors	10	800	87	250
(*a*) Syringomyelia	2	700	100	400
(*b*) Dorsal tumor with spinal-block cisterna	1	...	...	200
Lumbar	1	...	...	800
6. Epilepsy	7	200	75	100
7. Cerebral edema				
(*a*) Alcoholism	4	150	87	137
(*b*) Traumatic concussion (increased manometric reading)	9	150	87	100
8. Meningitis (serous type)	3	150	100	125
Tuberculous	1	...	...	150
9. Spinal-cord degenerations				
(*a*) Multiple sclerosis (cell-count average 18, 4 cases have paretic gold curve)	6	150	75	100
(*b*) Combined sclerosis	2	87	87	87
(*c*) Diffuse myelitis	1	...	...	75
(*d*) Spinal muscular atrophy	1	...	...	500
10. Psychoses				
(*a*) Manic excitement (dental sepsis)	1	...	...	100
(*b*) Depression, anxiety features	3	125	87	100
(*c*) Anxiety hysteria and neurosis	7	125	87	100
(*d*) Organic psychosis	2	250	187	212
(*e*) Arteriosclerotic	2	200	100	150
11. Miscellaneous				
(*a*) Hydrocephalus	1	...	...	100
(*b*) After intraspinal serum	2	200	100	150

Normal fluids contain 25 to 75 mg. per 100 cc. or 0.005 to 0.015 cc. in 2 cc.

Borderline fluids contain 75 to 100 mg. per 100 cc. (0.015 to 0.02 cc. in 2 cc.). This slight increase in the protein content may or may not be significant. Cerebral arteriosclerosis, postepileptic seizure states, encephalitis, head injuries with cerebral edema, treated inactive neurosyphilis, psychoneurotic-like states with toxic foci, alcoholism, multiple sclerosis, degenerative spinal-cord conditions and other neurologic conditions at times give this borderline reading. This moderate increase in total protein we have found of value in differentiating between organic and functional conditions. A positive increase favors an organic diagnosis.

1. Neurosyphilis. (*a*) *Paresis.* In this group we have found the highest protein content with the exception of the meningitides, xanthrochromic fluids and neuronitis cases. A few readings are low, 87 mg. per 100 cc. the highest was 500 mg. per 100 cc. The average paretic fluid gives a reading of 200 mg per 100 cc. Under treatment one of the first evidences of serologic improvement is shown by the protein content coming to normal. The cell count becomes normal with the protein content but the Lange curve and Wassermann tests improve more slowly. We find protein estimations valuable in estimating improvement under treatment. In a few instances the protein content has increased under treatment, illustrating a poor serologic response. In these cases we have usually found some complicating factor present, such as a septic focus of infection.

(*b*) *Tabes Dorsalis.* The protein estimations in this group have not given high readings. The lowest in treated cases give normal readings the highest 175 mg. per 100 cc. It is well known that inactive tabes may give completely negative serologic findings. It is rare not to find the protein content increased in tabes and we have found it an aid in a questionable case where the Wassermann was negative.

(*c*) *Cerebrospinal Types.* This group consists of the meningovascular cases. The meningitic forms give the highest readings in this group. As a rule the total protein content is not as high as in the paretic group, ranging from 75 mg. to 275 mg. per 100 cc. An average is about 125 mg. per 100 cc. As a rule there is a prompt response to treatment and this is indicated by the protein reading becoming normal. We have frequently observed cerebrospinal-fluid protein increase in secondary syphilis as the earliest finding of neurosyphilis, when the Wassermann and gold curves were negative.

2. Cerebral Arteriosclerosis. This group includes nonsyphilitic thromboses, organic dementia, aphasics and so forth, usually old lesions. As a rule we find the protein content moderately increased In one instance, in which we found a 250 mg. per 100 cc., there was a complicating diabetes and a manic excitement.

3. Epidemic Encephalitis. In all the positive acute cases a moderate to a marked total protein increase was noted. In the chronic cases the protein content was frequently normal. The pathologic readings averaged, 125 mg. per 100 cc. No parallelism was seen between high-cell counts and excess protein. Sugar content readings have not been consistent. In this group at times this increase in protein content is the only positive serologic finding and its determination is often a valuable aid in diagnosis.

4. Acute Polyneuritis. In the low-grade toxic or infectious multiple or mononeuritis cases the protein content has usually been found only moderately increased, about 100 mg. per 100 cc.

(*a*) *Neuronitis or Central Neuritis.* In the acute neuronitis cases we have found our highest protein determinations, except meningitis, 1 case of paresis and 1 xanthrochromic fluid. The readings averaged 450 mg. per 100 cc.

5. Brain and Spinal-cord Tumor. The brain-tumor cases almost invariably showed a moderate increase in protein, about twice normal, 100 to 150 mg. per 100 cc. One case of syringomyelia with xanthrochromic fluid gave an extremely high content, 700 mg. per 100 cc., and one case of glioma with rupture by hemorrhage gave a high-protein reading. The cord tumors where obstructive give high readings as do other xanthrochromic fluids. One cord tumor with evidence of hydrodynamic block gave a lumbar reading of 800 mg. per 100 cc. and a cisterna magna reading of 100 mg. per 100 cc. We have not had the opportunity of comparing many fluids above and below tumors. Nearly all of these tumor cases were verified at operation or necropsy.

6. Epilepsy. These are all cases in which organic factors were suspected but none found except some complicating toxic factors, such as infection, alcohol and so forth. This group showed protein determinations slightly above normal. Following a convulsion the protein content has been more definitely increased.

7. Cerebral Edema. The alcoholics with mental symptoms have all shown increased protein content. The same applies to head injuries showing increased manometric pressure readings. This is a transudative protein excess. The protein readings are about twice normal in these cases.

8. Meningitis. The purulent meningitides give the highest readings, we have not made routine determinations where the spinal fluid was purulent. Serous meningitis has consistently shown two to three times normal protein content.

9. Degenerative Spinal-cord Diseases. (*a*) *Multiple Sclerosis.* Only a moderate increase in the protein content was found in these cases. Often the reading is normal. No relationship between colloidal-gold curves and increased protein content was seen.

(*b*) *Combined Sclerosis.* Slight increase in the protein content may be found, but the reading is more often normal.

(*d*) *Muscular Atrophy.* In one case only did we find a marked increase in the protein content.

10. Psychoses. In one manic excitement case with marked dental sepsis the protein content was twice normal. Numerous depressions have shown pathologic protein increase. Usually a coincidental arteriosclerosis or focal infection has been demonstrated but in a few agitated depressions and anxiety neuroses no organic cause for the protein increase could be found. We have assumed in these cases there was an abnormal circulatory state giving a transudative protein excess. We believe a pure anxiety state may at times show protein excess in cerebrospinal fluid. Organic dementia: Etiology undetermined. In this group with sensorium alterations giving an organic psychotic reaction the spinal-fluid protein invariably has shown pathologic increase.

11. Miscellaneous. One hydrocephalic fluid showed a moderate increase in the protein content. After Swift-Ellis intraspinal injections the spinal-fluid protein content is increased.

TABLE II.—COMPARISON OF RESULTS WITH THE DENIS-AYER METHOD.

No.	Diagnosis.	Our method, mg. per 100 cc.	Denis-Ayer method, mg. per 100 cc.
1	Paresis	400	356
2	Preparesis (treated case)	175	152
3	Preparesis (postmalaria treatment)	55	47
4	Paresis (postmalaria treatment)	100	83
5	Paresis	100	146
6	Paresis	200	220
7	Tabes dorsalis	60	60
8	Tabes dorsalis (treated case)	50	46
9	Congenital syphilis	25	46
10	Congenital syphilis	60	94
11	Syphilis (non-neurologic)	50	38
12	Syphilis (non-neurologic)	75	94
13	Syphilis (non-neurologic)	37	33
14	Syphilis (secondary stage)	100	94
15	Epidemic encephalitis (lethargic stage)	150	180
16	Multiple sclerosis (cells 10, paretic Lange)	150	153
17	Alcoholic polyneuritis	50	66
18	Senile dementia	62	82
19	Cerebral thrombosis	25	47
20	Epilepsy with narcolepsy	50	82
21	Tuberculous meningitis	150	220
22	Spinal-cord tumor (xanthrochromic)	800	780
23	Diagnosis not determined	100	41
24	Diagnosis not determined	50	too low to read
25	Diagnosis not determined	75	120

Comment. Our method of quanitative protein estimation based upon a volumetric reading of the total protein precipitate in cerebrospinal fluid is entirely different from other methods described. The Denis method[1] consists of precipitating the cerebrospinal-fluid protein with sulphosalicylic acid and measuring the turbidity colorimetrically against a known standard prepared from blood serum. We have tried to carry out our method, using sulpho-

salicylic acid, but find the protein precipitate to be in such a finely divided suspension as to be centrifuged into the capillary tube only with difficulty. Through the coöperation of Dr. W. B. Moody, pathologist for the Nebraska Methodist Hospital, we have had the opportunity of comparing the results obtained by our method with the Denis-Ayer[2] method. Table II gives the results of the comparative determinations.

We are inclined at the present time to place the normal reading by our method higher than Denis and Ayer who believe the upper limit of normal to be 40 mg. per 100 cc. Our figures check very closely with the table given in their first[1] article. The greatest variation between the two methods is found in the low readings. It is difficult to determine an accurate reading with either method when low-protein content is present, but this does not alter the value of the determinations where the protein content is in excess.

While our method is subject to slightly greater error than the Denis-Ayer determination, we believe it is a more practical procedure. It is sufficiently accurate for all clinical purposes and can be readily carried out in any office, whereas all other methods require expensive equipment and a rather difficult preparation of materials and can only be carried out in well-equipped chemical laboratories.

Summary. A simple practical method, which is clinically accurate, for the quantitative estimation of the total protein content in cerebrospinal fluid has been described. It is based upon the principle of precipitating the total protein by alcohol, acetic acid and heat and measuring the resultant precipitation volumetrically in capillary-tipped vaccine tubes and reading it in terms of milligrams per 100 cc.

The method in about 600 determinations has proved of definite clinical value. Definite evidence of organic neurologic disorders is obtained where qualitative globulin determinations are normal or doubtfully positive. In neurosyphilis the determination is valuable in estimating serologic improvement under treatment. Total protein determinations give one of the earliest findings of cerebrospinal involvement in systemic syphilis.

Normal readings vary from 25 to 75 mg. per 100 cc. The highest readings are seen in the meningitides, central neuritis, xanthrochromic fluids and general paresis. We believe certain socalled functional nervous disorders, such as anxiety neurosis, at times show protein excess in cerebrospinal fluid, probably a transudative excess. This observation needs further study and confirmation.

The results of our method compare favorably in accuracy with results obtained by the Denis-Ayer determination.

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A NEW TABLE FOR LACTOSE (MILK OR URINE) AND GLUCOSE (BLOOD OR URINE) CALCULATION, WITH NOTES ON THEIR ESTIMATION.

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In previous papers[1,2] a simplified Shaffer-Hartmann method[3] has been offered. The same reagents and similar technique serve for estimation of glucose in both blood and urine. On the basis of the modification suggested by us a table[2] was constructed which gives a direct reading of the percentage of glucose in blood or urine, corresponding to the cubic centimeters of sodium thiosulphate solution used for titration. This method has given such good satisfaction that the author has adopted the same procedure for estimation of lactose. The table has been extended so as to include all percentages of lactose in milk and urine.

Since the details of the method are the same for both lactose and glucose of urine, the estimation can be made in accordance with the following directions even before qualitative tests have been performed to determine whether the particular sugar present is glucose or lactose.

Technique.—Measure exactly 1 cc. of urine into a 50-cc. flask, fill to the mark with water and mix. Depending on the concentration of the sugar in the urine take 5, 2 or 1 cc. of the dilute mixture for estimation. If the qualitative test (see note) does not show marked reduction, take 5 cc., but 2 cc. if there is strong reduction. When in doubt run two tubes (8 by 1 inch test tubes), measuring into one exactly 5 cc. and into the other 2 cc. (add to this 3 cc. of water). Add exactly 5 cc. of Shaffer's microcopper reagent and mix. Plug the tubes loosely with cotton, and place them in a boiling water bath. Occasionally glucose is present in such large amount that it is necessary to use 1 cc. of diluted urine (+ 4 cc. of water) for estimation.

After fifteen minutes heating remove the tubes from the bath and cool them rapidly to room temperature. Add 5 cc. of normal sulphuric acid, mix and cork loosely. After one minute titrate the iodin left in the solution using our special standard thiosulphate solution. When the color becomes pale yellow, add 0.5 to 1 cc. of 2 per cent starch solution and titrate cautiously to the disappearance of the starch-blue (leaving a copper-blue) color. When near the endpoint, shake well after the addition of each drop. The titration must be finished within twenty-five minutes after taking the tube from the bath.

Calculation. This consists merely in reading from the table opposite the cubic centimeter of thiosulphate used for titration the percentage given in the proper column. If the sugar present has been shown to be lactose, read from column L5 or L2 according to whether 5 or 2 cc. of dilute urine was used for estimation. If glucose is present, read from column U5, U2 or U1.

Note on the Qualitative Test. In doing the routine test use 5 cc. of Benedict's reagent and 0.3 cc. of urine, and heat for just five minutes in a boiling bath. Under these circumstances a greenish tinge is observed in the reduction mixture (even if there is considerable cuprous oxid in suspension) when less than 1.5 per cent of glucose (or a corresponding concentration of lactose) is present. This result indicates that 5 cc. of diluted urine is to be used for the estimation.

Effect of Urinary Constituents. Protein in moderate amount causes no appreciable error in the estimation. The slight reduction given by normal urine may be allowed for by deducting 0.1 (glucose) or 0.15 (lactose) from the percentage figure.

Note on Blood-sugar Estimation. Exactly the same technique is used for blood except that 5 cc. of protein-free filtrate (secured by Folin's[4] tungstic-acid method) without further dilution is taken for estimation. The per cent of glucose is found in column B of the table.

Estimation of Lactose in Milk. First remove protein with tungstic acid (as suggested by Shaffer) as follows: Measure exactly 2 cc. of milk into a 100 cc. flask, add 10 cc. of water then exactly 1 cc. of 10 per cent sodium tungstate solution and 1 cc. of $\frac{2}{3}$ normal sulphuric acid. Shake well and let it stand ten minutes. Fill to the mark, mix and filter. Measure exactly 2 cc. of filtrate into a large test tube. Add 3 cc. of water and 5 cc. of microcopper reagent, mix and plug the tube with cotton. Continue the method as described above.

Calculation. Find the per cent of lactose in column L2 opposite the cubic centimeter of thiosulphate used for titration.

Discussion. The lactose figures of the table were secured by making a large number of estimations on solutions of pure lactose.* The purest lactose obtainable was used ($C_{12}H_{22}O_{11}.H_2O$, Pfanstiehl). Anhydrous lactose was prepared by the author by recrystallization of commercial C.P. lactose, and was proved to be satisfactory by estimation by the Munson-Walker method. Several concentrations of this lactose gave the same estimations by our new method as were given by corresponding solutions of the hydrous lactose. The table gives figures for per cent of *anhydrous* lactose.

The figures of the table agree very closely with the curves for

* The author wishes to express his gratitude to Messrs. W. P. Holbrook, M. R. Eby, and F. Trotman who made a considerable number of estimations for the purpose of confirming the figures of the table.

reduction by lactose (constructed on the basis of the author's estimations). A comparison of the lactose with the glucose figures of the table shows that on the average 1.7 gm. of lactose have the same reduction effect as 1.0 gm. of glucose (the lactose equivalent being 1.66 to 1.68 for the more concentrated solutions, 1.69 to 1.71 for those of medium concentration in the middle of the table, and 1.72 to 1.78 for the most dilute solutions at the beginning of the table).

The estimations that were made on milk agreed well with the results by the Munson-Walker method.

Reagents.† (1) Standard Sulphuric Acid. The $\frac{N}{1}$ solution may be purchased, if one is not used to checking standard solutions. Prepare the $\frac{2}{3}$ normal solution by diluting 100 cc. of the N/1 acid with 50 cc. of distilled water.

(2) Sodium Tungstate Solution. C.P. tungstate should be used, and it should go into solution readily. The reagent must be tested for excess of carbonate as follows: To 5 cc. of the solution add a drop of methyl orange and some distilled water, then titrate with the $\frac{2}{3}$ normal acid until the yellow color changes to a slightly reddish-yellow. Between 3.0 and 3.3 cc. should be required. If the titration is greater add twice normal sulphuric acid (made by diluting about 11.5 cc. C.P. acid to 200 cc.) in sufficient amount to the whole batch of 10 per cent tungstate to bring its alkalinity down to the proper limits. Mix and titrate again.

(3) Starch Solution. This should be made every month. We prefer "soluble starch." Mix about 2 gm. of starch with 10 cc. of water and pour it into 90 cc. of boiling water; mix and boil one minute. Add a few drops of toluol as a preservative.

(4) Microcopper Reagent. Each constituent should be dissolved separately.

(*a*) 40 gm. C.P. anhydrous sodium carbonate (or 47 gm. pure monohydrated carbonate) in 400 cc. warm distilled water.

(*b*) 5 gm. C.P. copper sulphate (crystals that have not effloresced) in 100 cc water.

(*c*) 7.5 gm. pure tartaric acid in 100 cc. of water.

(*d*) 0.7 gm. pure potassium iodate (weighed accurately) in 100 cc. water.

(*e*) 10 gm. pure potassium iodid in 100 cc. water.

(*f*) 18.4 gm. pure *neutral* potassium oxalate in 100 cc. water.

When all are dissolved, mix (*c*) with (*b*), and pour the mixture slowly (with stirring) into (*a*). Combine (*d*), (*e*) and (*f*) and pour at once into the carbonate-copper mixture. Transfer to a liter measuring flask. Rinse all the dissolving beakers with small portions of water. When cooled to room temperature fill to the mark and mix well. Keep the reagent in a tightly corked bottle. A little sediment will be deposited; use the clear top liquid for estimations.

† The Shaw Supply Company (Portland, Tacoma and Seattle) will supply ready prepared solutions of guaranteed quality for the method.

If the chemicals are pure, the reagent run as a control will give the same titration, whether heated in a bath for fifteen minutes or not heated. With each new batch of reagent run a heated control and compare it with the unheated.

(5) STANDARD THIOSULPHATE. Dilute thiosulphate does not keep well. Prepare a stock solution of sodium thiosulphate a little stronger than $\frac{N}{10}$ (dissolve about 26 gm. of the crystals in about 1 liter of distilled water) and let it stand two days.

Dilute exactly 5 cc. to 100 cc. in a measuring flask and mix. Use this for titrating a control (5 cc. copper reagent and 5 cc. water treated with 5 cc. $\frac{N}{1}$) sulphuric acid, following the directions given above for the method of titration. The amount used will be less than 19.5 cc. When duplicate titrations agree within 0.1 cc., prepare a dilution of the stock thiosulphate such that exactly 19.5 cc. will be required for the titration of a control. For example, if 19 cc. of dilute thiosulphate were used, it will be necessary to dilute 5 cc. of the stock solution to 102.6 cc. (that is, $\frac{19.5}{19.0} \times 100$). First dilute the 5 cc. to 100 cc., then add the 2.6 cc. with a reliable pipette. Mix thoroughly. This ratio of dilution should be determined by similar titration of a control once in two weeks. Prepare the dilute solution each day that estimations are made. This is our modified standard thiosulphate, referred to in the technique. Keep the stock solution in a brown bottle well corked, set away where it will not get warm; under these conditions it keeps well (but weakens very slowly).

Note. The titration value of different samples of microcopper reagent, when accurate $\frac{N}{200}$ thiosulphate solution is used, is not always the same, although the variation is slight. We find that this value is close to 19.5 cc., therefore, we have taken this figure as the average titration value. Our table is based on this fact. Varying the amount of iodate in the reagent by inaccurate weighing changes the titration value.

The question may be raised: can accurate results be secured when a thiosulphate solution is used which is not exactly $\frac{N}{200}$? We have investigated this carefully and find that the results by our modified method are practically identical with those by the original Shaffer-Hartmann method (see data and the explanation for this surprising accuracy in our first paper[1]).

Summary. (1) A complete table is furnished which gives a direct reading of the percentage of sugar (glucose of blood and urine, also lactose of milk and urine) corresponding to the cubic centimeter of the special sodium thiosulphate solution used for titration. This table can be used only with the author's modification of the Shaffer-Hartmann method.

(2) Lactose of milk or urine can be estimated very easily and accurately with the same reagents and technique as for the estimation of glucose in blood and urine.

PER CENT SUGAR CORRESPONDING TO CUBIC CENTIMETER THIOSULPHATE USED FOR TITRATION.

Cc.	L2.	L5.	U1.	U2.	U5.	B.
19.2	0.50	0.20	0.34	0.17	0.07	0.014
19.0	0.63	0.25	0.53	0.26	0.11	0.021
18.8	0.75	0.30	0.71	0.35	0.14	0.028
18.6	0.85	0.34	0.88	0.44	0.18	0.035
18.4	0.97	0.39	1.05	0.53	0.21	0.042
18.2	1.08	0.43	1.21	0.61	0.24	0.048
18.0	1.20	0.48	1.37	0.69	0.27	0.055
17.8	1.31	0.52	1.51	0.76	0.30	0.061
17.6	1.42	0.57	1.64	0.82	0.33	0.066
17.4	1.53	0.61	1.77	0.88	0.36	0.071
17.2	1.65	0.66	1.90	0.95	0.38	0.076
17.0	1.75	0.70	2.04	1.02	0.41	0.082
16.8	1.87	0.75	2.18	1.09	0.44	0.087
16.6	2.00	0.80	2.32	1.16	0.46	0.093
16.4	2.11	0.84	2.46	1.23	0.49	0.099
16.2	2.23	0.89	2.60	1.30	0.52	0.104
16.0	2.35	0.94	2.73	1.36	0.55	0.109
15.8	2.47	0.99	2.85	1.43	0.57	0.114
15.6	2.57	1.03	2.98	1.49	0.60	0.119
15.4	2.68	1.07	3.10	1.55	0.62	0.124
15.2	2.78	1.11	3.22	1.61	0.65	0.129
15.0	2.88	1.15	3.36	1.68	0.67	0.134
14.8	2.98	1.19	3.49	1.75	0.70	0.140
14.6	3.10	1.24	3.64	1.82	0.73	0.146
14.4	3.20	1.28	3.78	1.89	0.75	0.151
14.2	3.32	1.33	3.92	1.96	0.78	0.157
14.0	3.45	1.38	4.05	2.02	0.81	0.162
13.8	3.58	1.43	4.17	2.09	0.83	0.167
13.6	3.70	1.48	4.30	2.15	0.86	0.172
13.4	3.80	1.52	4.43	2.21	0.89	0.177
13.2	3.92	1.57	4.56	2.28	0.91	0.182
13.0	4.05	1.62	4.70	2.35	0.94	0.188
12.8	4.15	1.66	4.84	2.42	0.97	0.194
12.6	4.25	1.70	4.99	2.49	1.00	0.200
12.4	4.35	1.74	5.12	2.56	1.02	0.205
12.2	4.47	1.79	5.25	2.63	1.05	0.210
12.0	4.57	1.83	5.37	2.69	1.07	0.215
11.8	4.67	1.87	5.51	2.76	1.10	0.220
11.6	4.78	1.91	5.65	2.83	1.13	0.226
11.4	4.89	1.96	5.80	2.90	1.16	0.232
11.2	5.00	2.00	5.93	2.96	1.19	0.237
11.0	5.10	2.04	6.05	3.03	1.21	0.242
10.8	5.20	2.08	6.18	3.09	1.24	0.247
10.6	5.30	2.12	6.31	3.16	1.26	0.252
10.4	5.40	2.16	6.44	3.22	1.29	0.257
10.2	5.50	2.20	6.57	3.28	1.31	0.263
10.0	5.60	2.24	6.70	3.35	1.34	0.268
9.8	5.70	2.28	6.85	3.42	1.37	0.274
9.6	5.80	2.32	6.98	3.49	1.40	0.279
9.4	5.90	2.36	7.12	3.56	1.42	0.285
9.2	6.00	2.40	7.24	3.62	1.44	0.289
9.0	6.10	2.44	7.35	3.67	1.47	0.294
8.8	6.20	2.48	7.46	3.73	1.49	0.298
8.6	6.30	2.52	7.57	3.79	1.51	0.303
8.4	6.40	2.56	7.69	3.84	1.54	0.307
8.2	6.50	2.60	7.79	3.89	1.56	0.312
8.0	6.62	2.65	7.90	3.95	1.58	0.316
7.8	6.73	2.69	8.01	4.00	1.60	0.320
7.6	6.85	2.74	8.12	4.06	1.62	0.325
7.4	6.95	2.78	8.25	4.12	1.65	0.330

Cc.	L2.	L5.	U1.	U2.	U5.	B.
7.2	7.07	2.83	8.38	4.19	1.67	0.335
7.0	7.20	2.88	8.50	4.25	1.70	0.340
6.8	7.30	2.92	8.64	4.32	1.73	0.346
6.6	7.42	2.97	8.78	4.39	1.76	0.351
6.4	7.55	3.02	8.92	4.46	1.78	0.357
6.2	7.65	3.06	9.07	4.53	1.81	0.363
6.0	7.75	3.10	9.21	4.61	1.84	0.368
5.8	7.87	3.15	9.36	4.68	1.87	0.374
5.6	8.00	3.20	9.50	4.75	1.90	0.380
5.4	8.10	3.24	9.64	4.82	1.93	0.386
5.2	8.20	3.28	9.78	4.89	1.96	0.391
5.0	8.32	3.33	9.92	4.96	1.98	0.397
4.8	8.43	3.37	10.06	5.03	2.01	0.403
4.6	8.55	3.42	10.20	5.10	2.04	0.408
4.4	8.65	3.46	10.34	5.17	2.07	0.413
4.2	8.75	3.50	10.48	5.24	2.10	0.419
4.0	8.85	3.54	10.61	5.31	2.12	0.424
3.8	8.95	3.58	10.75	5.38	2.15	0.430

L 2—Per cent anhydrous lactose if 2 cc. is used for estimation.
L 5—Per cent anhydrous lactose if 5 cc. is used for estimation.
U 1—Per cent anhydrous glucose if 1 cc. of diluted urine is used.
U 2—Per cent anhydrous glucose if 2 cc. of diluted urine is used.
U 5—Per cent anhydrous glucose if 5 cc. of diluted urine is used.
B —Per cent anhydrous glucose in blood.

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A GRAPHIC STUDY OF THE MUSCULAR ACTIVITY OF THE COLON, WITH SPECIAL REFERENCE TO ITS RESPONSE TO FEEDING.

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That some sort of relationship exists between the ingestion of food and defecation in normal man and in animals has been frequently observed. Every clinician has noted the urgent desire to defecate almost immediately after eating in cases of diarrhea and the abdominal distress and cramps during or immediately after a meal when less acute irritation exists. These clinical observations indicate that the ingestion of food has a stimulating effect upon the muscular activity of the colon.

The relationship between taking of food and increase in muscular

activity of the bowel has been mentioned by a number of observers. Hertz[1] (1909) found by making hourly tracings from the fluoroscopic screen after a bismuth meal in man, that apart from meals, progress through the colon was slow, but after each meal there was perceptible progress, more occurring during the dinner hour than in the previous four hours.

Cannon[2] (1911) makes passing mention of the probable relationship between the ingestion of food and defecation.

Barclay[3] (1913) observed the "mass movement" first described by Holzknecht[4] (1909) shortly after feeding an additional bismuth meal. Hertz[5] (1913) found in Roentgen ray observations on man, that the ileocolic sphincter normally held back the content in the terminal ileum for considerable periods of time, and that it relaxed at infrequent intervals. Further, peristalsis was never very active in the lower end of the ileum except during and immediately after meals. It was then that the greater part of the content entered the cecum. In further Roentgen ray observations on normal men Hertz[6] (1913) investigated the relationship between the ingestion of food and colonic activity. He observed in two out of six normal individuals, the "mass movements" of Holzknecht shortly after eating; in a third the mere sight of food seemed to produce the phenomenon. He also observed it in a woman with mucomembranous colitis.

One of us observed this "mass movement" in a girl with a mucomembranous colitis, when there was no relationship to feeding. In this instance the barium shadow was seen to pass with great rapidity from the upper third of the ascending, across the transverse colon to the splenic flexure where a small depot of barium was met. Then the entire mass passed downward in a continuous movement, into the sigmoid, pelvic colon and rectum. The entire movement did not consume more than a minute. Hertz[6] corroborates Holzknecht's conclusions that, this "mass movement" constitutes the normal movement in the colon and that it occurs three or four times a day; the colon remaining entirely inactive during the rest of the time. Hertz concludes that the chief stimulus for this movement is the entry of food into the stomach. This he terms the gastrocolic reflex.

Schwarz[7] (1911) claims that the human colon is never entirely at rest but always show some movements. Zondek[8] (1920) studied colonic activity by direct observation, eight days after the insertion of a celluloid window in the belly wall of dogs. He observed peristaltic movements that occurred with marked regularity about every thirty seconds. During starvation this peristalsis was slowed. The taking of food, however, produced marked stimulation of it.

Our results were obtained by methods that approximated normal conditions as nearly as possible. Dogs were used in which permanent fistulæ of stomach and colon had been established some weeks

before the observations were made. They were normal in every other way, being vigorous and apparently unmindful of their fistulæ. The dogs easily became accustomed to lying on the table for long periods of time, suffering no pain or discomfort.

Contractions of the colon were recorded from a sausage-shaped rubber balloon filled with water and introduced into the viscus through the fistula. The balloon was connected through a pear-shaped flask with a Brodie[9] bellows recorder, which traced the contractions on a slowly moving drum. The water pressure within the balloon was never sufficient to distend its fairly thick walls, so that the colon was not subjected to any active distention.

The balloons were roughly classified as small, medium and large; the medium-sized balloons had approximately the same diameter as the dog's stool; the small ones were less and the large ones greater in diameter than the stool.

The animals were regularly fed once a day at the same hour except on experimental days. The food consisted of table scraps.

The method here used for studying the activities of the colon has several distinct advantages. The results are not obscured or modified by anesthesia or recent operative procedures. Continuous graphic records showing all gradations of muscular activity can be obtained over long periods of time by it. Repeated observations on the same animal can be made under constant or varying conditions as to size of balloon and colon content.

Such studies as we have been able to find in the literature on the activity of the colon have been made under anesthesia and acute operations, by means of Roentgen rays or by ocular observations through a window in the belly wall. Anesthesia and operations themselves markedly affect the contractions. The shadows cast upon a fluoroscopic screen or sensitized plate, show only the gross changes in tonus and the larger contractions and do not give a continuous graphic record of the muscular activity of the gut wall. Further, the interpretations of the more or less fleeting observations on the fluoroscopic screen are dependent upon and vary with the individual making them. The use of a transparent window in the belly wall offers opportunity for more accurate observations but like the Roentgen ray, fails to show the finer gradations in activity and furnishes no graphic record.

In addition to the experiments on dogs, tracings were also made from the empty distal colon of men by means of a short (7 cm.) condom balloon inserted through a sigmoidoscope and connected with the same recording apparatus used in the dog experiments. The column of fluid was adjusted so as to fill the balloon but not distend it.

In the dog experiments the movements were studied with the colon full, empty and content unknown. The colon was considered normally full when the dog had not defecated during the twenty-four hours preceding or when the dog had a stool immediately

after an experiment. The colon was considered empty when the dog defecated just before the experiment or when the gut was flushed through the fistula with warm tap water or isotonic magnesium sulphate solution.

After inserting the balloon into the dog's colon there is nearly always a period of high tonus with active rhythmic contractions due to mechanical stimulation. This usually lasts about one hour. A continuous tracing was always made for two to five hours, to establish a normal, before feeding. The dogs were fed graham crackers or dog biscuit and in some instances meat; the tracing was continued for a considerable time after the feeding.

The normal muscular activity of the colon in dogs is very irregular. It consists chiefly of marked variations of tonus with or without superimposed contractions which occur most frequently when the tonus is high. The periods of high tonus often recur at regular intervals of fifteen to thirty minutes and usually last from five to fifteen minutes.

Variations from the above description occur, respresenting all degrees of activity from almost continuous high tonus with short periods of relaxation to long periods of inactivity with short infrequent contractions.

Such conditions as a full bowel preceding defecation or the introduction of a large balloon always increased the activity of the colon. Increased activity also followed the introduction of isotonic magnesium-sulphate solution through the fistula. These observations indicate that conditions within the lumen are potent factors in determining its activity. In no instance did we find the colon in a condition of complete inactivity as described by Holzknecht.[4] Even with the bowel completely emptied by flushing or defecation and with a small balloon in the lumen, there was always some activity. We do not believe the presence of the balloon produced this activity as it was smaller than the average stool, smoother, softer and less irritating than the usual colon content. No consistent differences in activity were demonstrable whether the balloon was inserted 5 or 15 or more inches from the appendix.

The effect of feeding upon the muscular activity of the colon was studied in 43 experiments on five dogs, and in 3 experiments on three human subjects.

In 37 of the 43 experiments the dogs were fed by mouth and ate the food greedily. Of these, 20 showed a marked increase in the activity of the colon. In 17 no definite change occurred. In 14 of these 17 negative experiments a small balloon was used (diameter less than dogs normal stool). In 11 of these the bowel was empty, the content having been flushed out or evacuated normally just before the experiment. While in 3 the content of the bowel was unknown. In the remaining 3 negative experiments the bowel was so active and changes in tonus and contractions so marked that any effect of feeding was masked.

In the positive experiments a definite change in the activity of the bowel occurred within half to several minutes after the feeding was begun. This consisted of a definite increase in tonus which was usually sustained for a period of ten to twenty minutes (Fig. 1, Tracing *B*); sometimes lasting an hour or more, (Fig. 1, Tracing *A*). Active contractions were frequently superimposed upon the tonus change but not invariably so. In numerous instances the dog defecated as soon as released. When this occurred or when a

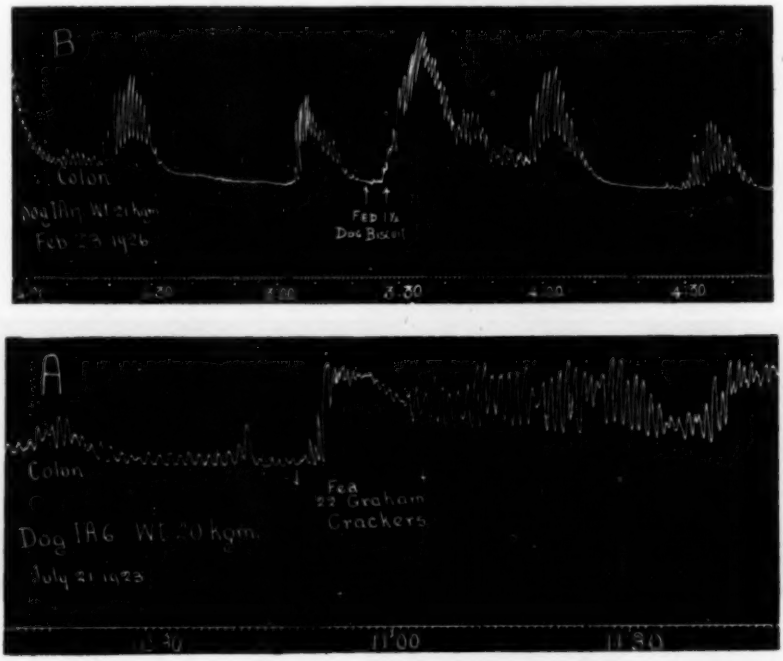

FIG. 1.—*Tracing A.* Positive result; Dog IA6, weight 20 kg; July 21, 1923; medium-sized balloon; bowel content unknown; balloon 25 x 140 mm.; capacity, 48 cc.; bellows 60 x 60 mm.; kymograph speed, 5 mm. per minute. *Tracing B.* Positive result; Dog IA17; weight 21 kg; February 23, 1926; medium-sized balloon; bowel full; large stool ten minutes after experiment ended; balloon 28 x 165 mm.; capacity, 64 cc.; bellows 60 x 60 mm.; kymograph speed, 3 mm. per minute.

large balloon was used the increase in activity was marked, with rapidly recurring periods of high tonus and frequently a marked increase in the number or extent of contractions.

In some experiments we were able, by repeated feedings, to produce the effect three or four times. In others there was no repetition of the effect with additional feedings.

More careful standardization of the conditions of our experiments such as the content of the colon and the size of balloon gave us more accurate information about the factors concerned in the

production of the effect and enabled us to explain the negative results that had been obtained. We found by emptying the bowel and using a small balloon, that the feeding effect was consistently absent. (Fig. 2, Tracing *A*). On the other hand with the bowel normally full and using a small or medium-sized balloon the feeding effect was consistently present. By using a large balloon with the bowel full, irregular results were obtained. In these instances the bowel activity was so great that the effect of feeding was often masked.

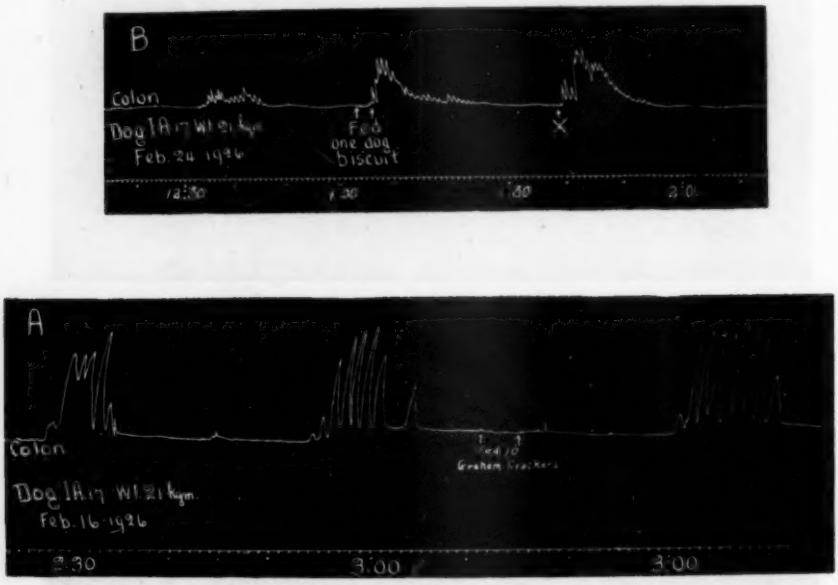

FIG. 2.—*Tracing A.* Negative results; Dog IA17; weight 21 kg; February 16, 1926; small balloon; bowel empty; colon flushed out with tap water before experiment; balloon 22 x 140 mm.; capacity, 35 cc.; bellows 45 x 60 mm.; kymograph speed, 6 mm. per minute. *Tracing B.* Possible psychic effect; Dog IA17; weight 21 kg; February 24, 1926; positive effect of feeding followed at (X) by a second increase in activity when the attendant entered the room; medium-sized balloon; bowel full; stool fifteen minutes after experiment ended; balloon 26 x 150 mm.; capacity, 55 cc.; bellows 60 x 60 mm.; kymograph speed, 3 mm. per minute.

In the experiments on men a similar effect was obtained, all three tracings showing a very definite increase in tonus (Fig. 3).

Effect on Colon Activity of Feeding through a Gastric Fistula. Three dogs with gastric fistulæ were used in this group of six experiments. The colon movements were recorded as before. In these experiments a mush of graham crackers and water was introduced into the stomach through the gastric fistula. In no instance was an effect upon the colonic activity demonstrable (Fig. 4).

These findings indicate that this effect or reflex is not dependent upon distention of the stomach with food as was suggested by Hertz[6]

and that his term "gastrocolic reflex" is a misnomer. We consider it a feeding reflex.

It is interesting to note in connection with the last group of experiments, that additional feeding by mouth after introduction of food through the gastric fistula often failed to produce the customary reflex. We frequently observed that the activity of the

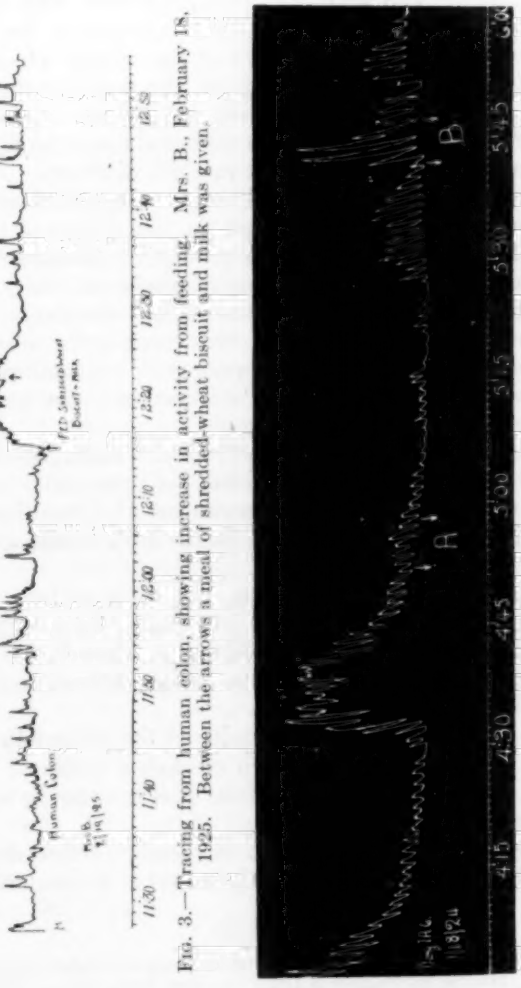

FIG. 3.—Tracing from human colon, showing increase in activity from feeding. Mrs. B., February 18, 1925. Between the arrows a meal of shredded-wheat biscuit and milk was given.

FIG. 4.—Effect of feeding through gastric fistula. Dog IA6; weight 20 kg; January 18, 1924. At *A*, 200 gm. of mush of graham crackers introduced into stomach through the fistula. At *B*, the dog was fed 10 graham crackers by mouth. Medium-sized balloon; bowel content unknown; balloon 24 x 160 mm.; capacity, 52 cc.; bellows 45 x 60 mm.; kymograph speed, 5 mm. per minute.

colon was apparently stimulated if the attendant who fed the dogs, entered the room during an experiment (Fig. 2, Tracing *B*). This occurred so frequently that it suggested the probability of a psychic stimulation.

The occasional negative result when the feeding was repeated by mouth, the consistently negative effect of feeding through gastric

fistula, together with the negative results of oral feeding after the introduction of food through the fistula and the apparent stimulation of colonic activity when the dog's keeper entered the room, all indicate that this is an appetite reflex, similar to the appetite reflex in gastric secretion, described by Pavlov.[10]

Because of the consistently negative results with a small balloon in an empty bowel and uniformly positive results with the bowel full, we conclude that the extent of the response in the bowel is not dependent alone on the intensity of the stimuli which initiate the reflex (feeding) but also depends on the responsiveness of the motor mechanism in the bowel itself. This latter varies widely from complete absence as occurs with the bowel empty to the marked exaggeration seen in conditions that produce diarrhea.

Such a mechanism indicates a nicely balanced equilibrium between the muscular activity of the colon and the functioning of the upper portion of the alimentary canal. A probable explanation for this may be found in Bayliss and Starling's[11] conclusion that, the peristalsis of the denervated gut was started by stimulation of local nerve plexuses by the presence of a stimulating agent in its lumen. Certainly our results indicate that some such mechanism controls the motor functions in the intact gut, modified by extraneous stimuli of which the feeding reflex is an example.

Summary. 1. The muscular activity of the colon, as shown by the method used here, consists chiefly of irregularly recurring changes in tonus, usually with superimposed contractions. The content of the colon is an important factor in determining the frequency and extent of these changes.

2. In none of these experiments was the colon entirely inactive.

3. When the bowel was normally full, feeding by mouth always increased its muscular activity. When the bowel was empty, feeding by mouth produced no obvious change, unless the recording balloon was of large size.

4. No change in the muscular activity of the colon followed the introduction of food into the stomach through a fistula.

5. In man a similar increase in activity was recorded by a balloon introduced into the sigmoid colon.

6. The evidence indicates that this is a feeding reflex, dependent upon appetite and the condition of the bowel as to content.

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REVIEWS.

REPRODUCTION IN THE RABBIT. By JOHN HAMMOND, M.A. (CANTAB.) School of Agriculture, Cambridge. With Foreword and Chapter on the Formation of the Corpus Luteum. By F. H. A. MARSHALL, F.R.S. Pp. 200; 20 plates. Edinburgh and London: Oliver and Boyd, 1925.

THIS is one of a series of specialized biological monographs being brought out by English research workers. The physiology of reproduction in rabbits has been observed in its many phases over a long period by the author, and the results of these observations are here set forth. There is a foreword by F. H. A. Marshall, whose physiology of reproduction is well known, he has also contributed the chapter on the formation of the corpus luteum. The subject is thoroughly covered, there being chapters devoted to all the major phases, including reproduction in the male. There are certain interesting endocrinological suggestions in the chapter on sterility. The book should interest anyone in obstetric work from a comparative physiological viewpoint. P. W.

THE THERAPY OF PUERPERAL FEVER. By PRIVATDOZENT DR. ROBERT KOEHLER, formerly Assistant of the Gynecological Department of the Krankenhaus Weiden (Director: PROF. DR. JOSEF HALBAN) in Vienna, Austria. American Edition prepared by HUGO EHRENFEST, M.D., F.A.C.S., Associate in Obstetrics, Washington University School of Medicine, Obstetrician and Gynecologist of the Jewish Hospital, St. Louis. Pp. 244; 27 illustrations. St. Louis: C. V. Mosby Company, 1925. Price, $4.00.

THIS monograph presents the teaching of the Halban Clinic in Vienna in regard to the prophylaxis and general therapy of puerperal sepsis, and a critical analysis of the results obtained with a large number of medical and chemical agents in this disease. One feels while reading the book that the German edition has had an able translation and sympathetic editing by Dr. Ehrenfest. A voluminous bibliography is appended.

The trend of the teaching is conservative and, in spite of some quoted literature, is quite in accord with modern American obstetric practice. The value of rectal examination during labor is emphasized, external preparation of parturients consists in applications of benzine, iodin and alcohol, and antepartum douches are not used. Koehler expects nothing from prophylactic immunizations, considers alcohol internally of no value. He uses saline solution extensively in treatment. It is difficult to accept the differentiation of the septic postabortal uterus and the septic puerperal uterus in regard to intrauterine instrumentation as given on page 57. Hysterectomy is limited to necrobiotic myomas and to cases of perforation. There is a full discussion of surgery, especially drainage, in peritonitis. Ligation for septic thrombophlebitis is condemned.

Medicinal treatment and chemotherapy comprise the second half of the book. The action of some thirty agents, dyes, salts or methods was observed, the case histories and appended temperature charts show the almost uniform failures of such methods. Concerning antiseptics it is stated "Doses that can be administered intravenously without undue danger, necessarily are so minimal that one could not hope to obtain their presence in the blood in a concentration sufficient to be effective." The author places little reliance on serums, vaccines, protein therapy and leucostimulants. Blood transfusion he finds of little value.

Although Koehler has offered no solution for this as yet unsolved problem, he has given us a very stimulating discussion of the subject, and a most thorough analysis of the many modern suggestions as to therapeusis. P. W.

A Synopsis of Medicine. By Henry Letheby Tidy, M.A., M.D., B.Ch., F.R.C.P., Assistant Physician to St. Thomas's Hospital; Physician to the Royal Northern Hospital. Fourth Edition. Pp. 1000. New York. William Wood & Co., 1925. Price, $6.00.

If a synopsis owes its value to a clear, orderly, systematic arrangement of essential facts, Tidy's work on Medicine, a companion volume to the Groves' Surgery, and the fourth edition in five years meets the requirement in admirable fashion. The reader cannot go through the volume without meeting many things which he has long forgotten—or never knew; and a full index and the arrangement of headings makes rapid reference easy. The newer matter includes diabetic metabolism and insulin therapy; the use of quinidin; and recent work on jaundice. One finds no reference to diphtheria toxin-antitoxin, to scarlet fever antitoxin, to basal metabolic study. But certainly for the man who must read as he runs, it is far better than running without the reading. L. G.

NOT SPEAKING OF OPERATIONS. By JOHN FINCH BARNHILL, F.A.C.S. Pp. 159; 3 illustrations. Boston: The Stratford Company, 1925. Price, $2.00.

THIS booklet "points out the fact that hospitals are not altogether places where misery and distress forever sit in darkness, as some seem to believe, but rather are they places where sunshine, hope and even joy are found in surprisingly large measure, and where optimism is a predominant trait, even among many who have been long ill and often hopelessly ill.

"This book also shows that a reasonable amount of talk among convalescents in hospitals, and those who have at some period or other 'done time' in a hospital is both sensible and helpful."

E. K.

ABDOMINAL AND PELVIC SURGERY FOR PRACTITIONERS. By RUTHERFORD MORISON, HON. M.A., D.C.L., HON. LL.D., M.B., F.R.C.S. Pp. 212; 9 illustrations. New York: Oxford University Press, American Branch, 1925.

THIS little book is one of the best that the reviewer has had occasion to read in many months. It presents the salient features of surgical diagnosis, with reference primarily to helping the patient and secondarily with a veiw to the interest that may or may not be present in the patient as a pathological specimen. When we recognize the fact that thousands of lives are lost from abdominal injuries and diseases because the operation was postponed until the patient was exsanguinated from hemorrhage or peritoneal insult became a general peritonitis or an intestinal obstruction had continued for forty-eight to seventy-two hours, a work of this sort appeals to one immensely. The author attempts and does most clearly show how to recognize early in their existence the sign posts that point to treatment. Throughout the entire work his statements are backed, illustrated and proven by innumerable case reports bearing on the subject at hand. The book is as interesting as a novel and very valuable from the standpoint of vital information. E. E.

DIAGNOSE UND THERAPIE DER GONORRHŒ BEIM WEIBE. By S. JESSNER. Leipzig: Curt Kabitzsch, 1925.

THIS little volume, which is hardly more than a pamphlet, is the twenty-fifth of a series devoted to skin and venereal subjects. It embraces in a clear but elementary manner the main points in our present knowledge of the diagnosis and treatment of gonor-

rhea in the female. After considering gonorrhea of the vulva and pelvic organs, the rarer forms of gonorrheal infection are described, including affections of the muscles and tendons, heart, nervous system and eye. The book will have little appeal to American physicians, who can get all that this volume contains from any standard textbook. F. B.

DIABETES AND ITS TREATMENT BY INSULIN AND DIET. By ORLANDO H. PETTY, M.D., Professor of Diseases of Metabolism in the Graduate School of Medicine, University of Pennsylvania and WILLIAM H. STONER, M.D., Associate Professor of Biochemistry, Graduate School of Medicine, University of Pennsylvania. Second edition. Pp. 133; 9 illustrations. Philadelphia: F. A. Davis Company, 1925.

THIS volume is for the laity. It is similar to the books of its type, which are available, in that it describes what diabetes is and its treatment. It discusses diets, gives tables of food values and recipes.

It is written in a clear lucid style, and certain it is that patients who read this book will have a comprehensive idea of the disease and the objects of treatment.

The authors are enthusiastic about the results obtained in the treatment of hypertension by the use of "salt-free" diets. From the figures they give apparently they obtained better results by this treatment than the reports from most clinics would indicate.

The reviewer believes that it would have been advisable to mention no references, other than to refer to Dr. Banting's work.

L. J.

THE CHEMISTRY AND PHYSIOLOGICAL PROPERTIES OF THE INTERNAL SECRETIONS. By E. C. DODDS and F. DICKENS, University of London and Bland-Sutton Institute of Pathology, Middlesex Hospital. Pp. 201; 4 illustrations. London: Humphrey Milford: Oxford University Press, 1925.

AN excellent book in a new field, covering the chemistry of the active principles of the endocrine glands. It contains a historical survey and includes all the recent advances in the field. The principal chapters are on the secretions of the pancreas, pituitary, thyroid, ovaries and suprarenal glands, which have a well-established active principle. Deserved emphasis is placed on the secretion of the ovarian glands and the possibilities of its importance. Under Physiologic Properties in each chapter is an excellent résumé of the physiologic action of each of the active principles.

W. K.

AN INTERMEDIATE TEXTBOOK OF PHYSIOLOGICAL CHEMISTRY. By C. J. V. PETTIBONE, Medical School of the University of Minnesota, Minn. Third edition. Pp. 393. St. Louis: C. V. Mosby Company, 1925.

IN the third edition of this book the material has been increased and brought up-to-date. The book is rather elementary, with the usual chapters on foodstuffs, digestion, metabolism and excretion. Physical biochemistry is not stressed in any portion of the book.

Part II of the book contains the usual laboratory experiments with the most recent urine and blood analyses. W. K.

PHYSIOLOGICAL CHEMISTRY. By ALBERT P. MATHEWS, PH.D., Professor of Biochemistry, The University of Cincinnati. Fourth edition. Pp. 1233. New York: William Wood & Co., 1925.

THE growing tendency in our medical schools to regard physiologic phenomena from the physicochemical aspect is reflected in this valuable work, which, however, maintains in its proper perspective classical physiologic chemistry. The book is a treatise rather than a textbook, and may be recommended as an excellent guide for the worker in biochemistry. For the student of medicine, however, it is perhaps too exhaustive.

In addition to bringing the subject-matter up-to-date, the author has included some new material, notably the chapter on the skin and eye. Concerning the bibliographies at the conclusions of each chapter, it may be said that frequently important modern work is neglected while much of the earlier literature, chiefly of historical interest, is included. B. O.

THE MECHANISM AND GRAPHIC REGISTRATION OF THE HEART BEAT. By SIR THOMAS LEWIS, M.D., F.R.S., Physician of the Staff of the Medical Research Council and Physicians and Lecturer in Cardiac Pathology, University College Hospital, London. Third edition. Pp. 529; 400 illustrations. London: Shaw & Sons, 1925.

A NEW edition of the author's *Mechanism of the Heart Beat* is always an event for cardiologists, and the care with which the present revision has been made will amply repay a close survey on their part. As no small part of the new work that has been incorporated comes from the author's own laboratory, the statements can be relied upon as authoritative. The circus movement, discovered by Mines and Garrey, and applied to human cardiology by

the author, is discussed at length with its related problems in five chapters. His recent work on extrasystoles is responsible for a more extensive discussion of their origin; the nature of heart block gets a new chapter. The question of the independence of the excitation and contraction processes, to which Einthoven made strong objection in 1921, is mentioned (p. 51) but not discussed. As was pertinently remarked in the *Lancet* (September 19, 1925), "The general physician of today must be content to receive most of his mental nourishment in a predigested form, but for those who still prefer to masticate their own food, and are prepared to curtail the number of courses on the menu, a book such as this is invaluable." We agree that it holds a unique position in modern cardiology. E. K.

GYNECOLOGIC UROLOGY. By LYNN LYLE FULKERSON, A.B., M.D., F.A.C.S., Assistant Professor of Gynecology, New York Post Graduate Medical School. Pp. 227; 145 illustrations. Philadelphia: P. Blakiston's Son & Co., 1925.

ALTHOUGH most modern textbooks on gynecology offer a fairly comprehensive presentation of urology, it is possible that there may be a place and need for a small volume, such as this, devoted solely to endoscopy and diseases of the urinary system. The subject is covered fully, the chapters are well arranged and the bibliography attached to each chapter is a guide to original literature. The text is profusely illustrated but, although the illustrations are well chosen, the fact that so large a number are borrowed from books of a similar nature detracts from the value of the book in hand as an original offering. The discussion of endoscopy is detailed, and the author describes an ingenious modification of the Kelly cystoscope. P. W.

THE WRITING OF MEDICAL PAPERS. By MAUD H. MELLISH, Editor of the Mayo Clinic Publications. Second edition, revised. Pp. 168. Philadelphia and London: W. B. Saunders Company, 1925.

READERS of medical journals little realize the vast difference that so often lies between the printed article and the wretched stuff as presented to long-suffering editors. The reviewer, therefore, hails with delight the appearance of the second edition of Mrs. Mellish's book; perhaps it is a sign of an increasing desire on the part of would-be medical writers to learn how they may express their thoughts correctly, concisely, and withal, pleasingly. Certainly, they will find in this little book an excellent guide and helper.

A tendency of the author to dogmatize, the result in a measure of brevity of presentation, will be to the beginner a help, not a hindrance; good arrangement and complete indexing of the subject matter make it easy of access. R. K.

THE PATHOLOGY OF TUMORS. By E. H. KETTLE, M.D., B.S. (LOND.), Professor of Pathology and Bacteriology, Welsh National School of Medicine, Cardiff. 2d Edition. Pp. 285; 159 illustrations. New York: Paul B. Hoeber, Inc., 1925. Price, $5.00.

A HELPFUL manual for students of tumor pathology. The author, in Parts I and II, which deal with the general biology and pathology of tumors, respectively, presents practicably, the essential facts and more generally accepted opinions on the pathology of tumors without going into great detail. Part III briefly treats of the special pathology of tumors. Drawings rather than photomicrographs, giving the illustrations an ideal more than a real significance, are used. In this second edition, thirty-three new figures have been added, and the text has been carefully revised. J. G.

CEREBROSPINAL FLUID IN CLINICAL DIAGNOSIS. By J. GODWIN GREENFIELD, M.D., B.Sc., M.R.C.P., Pathologist to the National Hospital for the Paralyzed and Epileptic, and E. ARNOLD CARMICHAEL, M.B., CH.B., Resident Medical Officer, National Hospital for the Paralyzed and Epileptic. Pp. 272; 8 figures, including two diagrams. London, Macmillan & Co., Ltd., 1925.

THIS book is attractively and serviceably bound and is printed on a good grade of paper in easily read type. The subject matter is divided into three parts: Part I, on the nature and composition of the cerebrospinal fluid and its changes in disease; Part II, on the cerebrospinal fluid in certain diseases; Part III, on the technique of examination of the cerebrospinal fluid. The reviewer must take exception to the author's reason for placing the section on technique last, as it is not to be considered "the least important," but rather of equal importance with the rest of the subject matter. There is probably no body fluid, in the examination of which technique is of greater importance than in the case of the cerebrospinal fluid.

Part I considers the technique of lumbar, cisternal and ventricular puncture; the anatomy of the ventricles, spaces, and so forth, containing cerebrospinal fluid and the physiology of its production, absorption, and so forth, pathologic changes in the cytology and chemistry of the cerebrospinal fluid, with special chapters on colloidal reactions and Froin's syndrome.

This section is of interest principally to the specialist and the research worker, as much of the material is, in the present state of our information, of no clinical significance, but may become of value when we have learned how to use it. The notes on the technique of puncture are helpful, although one is given the impression that ventricular puncture at least is a much more simple procedure than is actually the case.

Part II considers the cerebrospinal fluid in meningitis and syphilis in detail, while other nervous diseases are grouped together. There is a separate chapter on some points in differential diagnosis. This section is excellent, and will be very useful to the clinician. Especially helpful is the chapter on differential diagnosis. A more detailed consideration of the special bacteriology of the cerebrospinal fluid would not be amiss in a work of this character, which in most particulars is so thorough. One feels that the cultural characteristics of the meningococcus at least should be specified, and possibly also of other organisms, such as the pneumococcus and the influenza bacillus, which frequently are associated with meningeal infection.

Part III, on the technique of examination of the cerebrospinal fluid, gives clear and definite directions for the various examinations, and is complete with the exception of the omission of the technique of the Wassermann reaction. Information should be given either here or in the chapter on syphilis, as to what technique was used, for without this information much of the data as to the degree of positivity loses its significance.

The illustrations are too few, and do not illustrate points of importance. It would be very helpful to have illustrations of the anatomic relationships of the ventricles and canal, pictures of meningococci, and so forth, in smears, and pictures or diagrams showing puncture needles in position.

The charts are good and the tables instructive, and the references are very complete. The authors are to be congratulated upon the thoroughness with which they have covered this subject and upon the production of a very interesting and instructive book.

L.

DEVELOPMENT OF OUR KNOWLEDGE OF TUBERCULOSIS. By LAWRENCE F. FLICK, M.D., LL.D., President of the White Haven Sanatorium Association; formerly Director of the Henry Phipps Institute. Pp. 783. Published by the author, Philadelphia, 1925.

THE history of tuberculosis which may serve well as an epitome of the history of medicine is traced from the ancient period of

vague suggestion down to the controversy concerning tubercle bacilli of human and of bovine origin which at the beginning of the present century at last defined in accurate detail the etiology of the disease. The author admits with reluctance that possible references to tuberculosis in writings which precede Hippocrates are vague and uncertain and then describes the abundant knowledge of the ancient Greeks. Throughout the volume there is evidence that tuberculosis has been the foremost scourge of European civilization. The story of tuberculosis is built up by a detailed review of the writings of those who have contributed to our knowledge of it and lengthy quotations are freely used. Under the author's guidance we pass through the long period in which, often with clear recognition of the symptoms of disease, there was groping effort to establish their relation and explain their origin and we proceed into the period following the Renaissance, when pathologic anatomy advanced the classification of disease and laid the foundation for physical diagnosis. Nevertheless there could be no clear definition of the domain of tuberculosis or of other infectious diseases until each was defined in relation to the microörganism which is its cause. The clear picture of tuberculosis drawn by Balye and by Laennec failed to prevent subsequent confusion. Virchow's contributions to the subject are fully described. Later we may follow the steps by which the discoveries of Villemin and Koch ended the time-honored controversies concerning the nature of tuberculosis.

To those who are engaged today in the study of tuberculosis the age-long controversy concerning the transmissibility of the disease has more than historic interest. The laws of Spain and of Naples enacted to prevent contagion in the eighteenth century are discussed, and the views of Sylvius, Morgagni, Hufeland and others who (with Laennec perhaps) believed that tuberculosis was contagious, and of Cullen, Portal and Rush, who denied its contagion, are described. Four chapters are given to the studies of Villemin upon animal inoculation and Koch's researches are cited. It is noteworthy that nearly a half century after the discovery of the tubercle bacillus there is still so much uncertainty concerning the mode of its transmission from one individual to another, that infection during adult life is maintained by some and denied by others. The author makes no attempt to review the research of the present century which has been concerned in part with the life history of the tubercle bacillus and the resistance of the host to it, but suggests that he may later undertake this task.

The book contains a vast store of information concerning tuberculosis otherwise not readily obtainable. It should be accessible to those who are engaged in the care of tuberculosis for they will find in it pleasure and profit. O.

FEEDING AND THE NUTRITIONAL DISORDERS OF INFANCY AND CHILDHOOD. By JULIUS H. HESS, M.D., Professor and Head of the Department of Pediatrics, University of Illinois College of Medicine; Member of Advisory Board, Children's Bureau, Department of Labor, Washington, D. C. Fourth revised and enlarged edition. Pp. 556; 42 engravings in the text and 1 full-page colored plate. Philadelphia: F. A. Davis Company, 1925.

THIS book, formerly known as the *Principles and Practice of Infant Feeding*, maintains the same splendid tone which made three previous editions so popular. Orderliness of arrangement, explicitness of instruction and a profusion of practical suggestions make it a most valuable handbook for both pediatrist and practitioner. Especially commendable is the discriminating choice of feeding methods and the clearness of the author's indications for these methods. A new chapter has been written about celiac disease, and new sections added on acidified milks, on feeding the older infant and preschool child, and on the food values of individual servings. The chapters on rickets and spasmophilia have been revised to include the many recently acquired ideas on these subjects.

S.

INSULIN AND ITS USE IN DIABETES. I. Physiology. By J. J. R. MACLEOD, M.D., of the Department of Physiology, University of Toronto. II. Clinical Section. By W. R. CAMPBELL, M.D., of the Department of Medicine, University of Toronto. Pp. 237; 7 illustrations. Baltimore: Williams & Wilkins Co., 1925. Price, $4.00.

THIS monograph, which originally appeared in *Medicine* last year, is one of the best summaries of our knowledge of insulin up to that time. The section on the physiology of insulin was written by Professor Macleod and deals with every phase of the subject in a clear and lucid style. The clinical section was prepared by Dr. Campbell. He discusses in a comprehensive manner when to use insulin, how to use insulin and conditions in which it is indicated and its dangers. There are chapters on respiratory metabolism, acidosis and allied subjects and how properly to diet a patient with diabetes. The bibliography at the end of the book includes all previous articles on insulin. Chapter XII, which deals with the diagnosis of diabetes mellitus seems quite incomplete.

The discussion of glycosuria due to conditions other than diabetes mellitus is not clear. In view of the importance of differentiating nondiabetic glycosuria from that of diabetes mellitus it would seem to the reviewer that it would have been profitable to have elaborated on this particular subject.

This book is recommended to all physicians who treat patients suffering from diabetes, first, because the subjects discussed should be known by those who use insulin and second because of the sound manner in which the subject is treated. L. J.

RECENT ADVANCES IN OBSTETRICS AND GYNECOLOGY. By ALECK W. BOURNE, B.A., M.B., B.CH. (CAMB.), F.R.C.S. (ENG.), Obstetric Surgeon to the Out-patients, St. Mary's Hospital; Senior Obstetric Surgeon, Queen Charlotte's Hospital; Surgeon to Out-patients, Samaritan Hospital for Women; Gynecologist to the Willisden Hospital. Pp. 331; 58 illustrations. Philadelphia: P. Blakiston's Son & Co., 1926. Price, $3.50.

WHAT constitutes an advance in any branch of medicine, and how long an idea may be considered to be recent is rather difficult to answer. In this small volume Dr. Bourne appears to have succeeded in reviewing and evaluating British literature of recent years in a most admirable manner. There are but few Continental or American references. His discussion of newer theories, methods and operations while presented briefly bears no resemblance to a collected series of abstracts nor to a copying of summaries and conclusions of many related articles.

Under obstetrics one finds puerperal sepsis, obstetric deaths, fetal mortality, hemorrhage, toxemias and the metabolism of pregnancy, and a broad-minded review of Cesarean section. Operative technique is presented under the general progress of gynecology, Rubin's and Sampson's work appear in sterility and endometrioma of the ovary. Roentgenology, electrotherapeusis and radiology are discussed by collaborating authors; these chapters are excellent.

P. W.

A TEXTBOOK OF PHARMACEUTICAL CHEMISTRY. By ARTHUR OWEN BENTLEY, PH.C., Director of the Department of Pharmacy, University College, Nottingham; and JOHN EDMUND DRIVER, M.Sc., A.I.S., Lecturer in Chemistry, University College, Nottingham. Pp. 456, with 6 illustrations. New York: Oxford University Press, 1925. Cloth. Price, $6.00.

THIS book is intended to assist the British student of pharmacy in preparing for examinations for degrees and licensure. Its purpose is to facilitate the identification of substances of the British Pharmacopœia, and the necessary information is given concisely and completely. It does not consider plant analysis or the synthetic derivatives of arsenic, mercury, bismuth, or silver. It should be

extremely useful to the British student, definitely less so to the American, though toxicologists and pharmacologists will find it valuable for its condensed information and analytical procedures regarding drugs and poisons commonly encountered in this country.

C. S.

RYALL'S OPERATIVE CYSTOSCOPY. By E. CANNY RYALL, F.R.C.S., Senior Surgeon to all Saints Hospital for Genitourinary Diseases, London, England. Pp. 46, followed by 115 plates, giving 670 original illustrations, 528 in colors. St. Louis: C. V. Mosby Company, 1925. Price, $25.00.

IT has long been an axiom in urology that cystoscopy cannot be taught. It must be learned by practice and experience. No spoken or written word will ever portray the remarkable views seen. It is here that Ryall's book enters an unoccupied field, for not even Wassildo's Atlas approaches this comprehensive work. It covers the subjects of anesthesia, ureteral, vesical and prostatic disease. Forty-six pages are devoted to technique and the description of the cases illustrated. This is delightfully brief, authoritative and often with valuable deductions drawn. Throughout this text easy reference is made to the 115 colored plates (each comprising 6 pictures) that compose the remaining nine-tenths of the volume. A most unique value lies in the serial nature of the pictures when from 2 to 54 illustrations show the successive step in treating an individual case. There is but one fault to find, that is, the absence of distinctive diagnostic differences between benign and malignant bladder neoplasms and one is left with the erroneous impression that fulguration cures all vesical tumors. The pictures—their accuracy, beauty and lifelike coloring, bespeak the optimum in lithographic art, while the volume as a whole represents workmanship of the very highest order from cystoscopic surgeon, artist and publisher.

A. R.

RADIOGRAPHY, A MANUAL OF ROENTGEN RAY TECHNIQUE, INTERPRETATION AND THERAPY. By CHARLES D. ENFIELD, M.D., F.A.C.P., Roentgenologist to St. Anthony's Hospital and Norton Memorial Infirmary, and so forth, Louisville, Ky. Pp. 299; 194 illustrations. Philadelphia: P. Blakiston's Son & Co., 1925. Price, $10.00.

THIS book contains twenty-three chapters, dealing with Roentgen ray history, physics, equipment, photography, preparation of patients, protection, interpretation and therapy. The author has committed himself to a worthy, but extremely difficult task, in

that his book is written for medical men who wish to do all of their own work, and not for roentgenologists. Such a book, however, should not attempt to deal with Roentgen ray therapy in seven pages and allow as much space as thirteen pages for dark room technique, and thirty-six pages for equipment and accessories. The interpretation of various lesions is very brief, probably because of the lack of space. The publishers are to be commended on the paper, print and illustrations. E. P.

ACUTE INFECTIOUS DISEASES—A HANDBOOK FOR PRACTITIONERS AND STUDENTS. By J. D. ROLLESTON, M.A., M.D. (OXON.), Senior Assistant Medical Officer, Grove Fever Hospital, London; Editor, British Journal of Children's Diseases; President, Section of History of Medicine, Royal Society of Medicine. Pp. 376; no illustrations. New York: Physicians and Surgeons Book Company, 1925.

THE diseases which are presented under this title, in their order of consideration, are as follows: Diphtheria, Vincent's angina, cerebrospinal fever, whooping cough, typhoid fever, paratyphoid fever, typhus fever, mumps, scarlet fever, measles, rubella, the fourth disease, erythema infectiosum, varicella, smallpox and, vaccination.

The book is laboriously written in an attempt to present full clinical accounts of the diseases considered. Brief historical notes, accounts of etiologic factors, and of the pathologic aspects of each disease are included. The material is presented in a well-arranged orderly fashion but lacks the inspiring style of a great teacher. The newer methods employing the effects of convalescent serum in the prevention and treatment of measles are properly emphasized and should serve to encourage their more general application.

The sections on the history, etiology and treatment of scarlet fever need revision in the light of the recent developments of our knowledge of this disease. Mention is made of the epoch-making work of the Dicks and of the use of Dochez's serum in treatment, yet in the section on treatment the statement is made, "Apart from the use of convalescent serum, or whole blood . . . scarlet fever . . . has no specific treatment." It is appreciated that the manuscript must have been written before the recent advances in scarlet fever were fully evaluated, but even in the dawning of knowledge of the true nature of the disease which was apparent before the printing, such a statement should have been rewritten, by one who had available a detailed report of the use of Dochez's serum in a limited number of patients. The author evades a direct statement of the etiologic factor in scarlet fever and

thus fails in presenting a true concept of the mode of spread and method of invasion of the virus.

Under the specific treatment of diphtheria it is difficult to see the justification for advocating divided doses of antitoxin on consecutive days.

The sections on the specific diagnosis of diseases of known etiology are weak. The technique of the diazo reaction is presented under typhoid fever, yet the methods of absolute diagnosis by culture are not detailed. The suggested use of monovalent serum in the treatment of cerebrospinal meningitis is to be commended, yet one can scarcely forgive the failure to mention culture of spinal fluid for diagnosis instead of the impracticable advocacy of "animal inoculation" when direct smear examinations fail.

A delightful feature of the book is the citation of liberal lists of well-selected references to original work which has served in the development of our knowledge of each of the diseases.

J. S.

ALLERGY, ASTHMA, HAY FEVER, URTICARIA AND ALLIED MANIFESTATIONS OF REACTION. By WILLIAM W. DUKE, PH.B., M.D. Pp. 339; 75 illustrations. St. Louis: C. V. Mosby Company, 1925. Price, $5.50.

AN interesting and valuable presentation of the subject, especially from the clinical standpoint.

In Part I, the author first reviews the field of experimental anaphylaxis. He next discusses the phenomena of natural hypersensitiveness, the nature of agents to which human beings are sensitive, and the contributory causes of reaction. The presentation of pollen disease is particularly complete. The various types of reaction that may occur in human hypersensitiveness are fully described, as are the methods of specific diagnosis. Then follows a description of the methods of specific, nonspecific and symptomatic treatment. In Part II, the author sees fit to describe under the head of allergy certain original observations on reactions caused specifically by the action of physical agents, such as light, heat, cold, mechanical irritation and others.

The book speaks for an extensive experience and careful observation on the part of the author in the field of allergic disease. There are cited many interesting and unusual cases that well illustrate the countless ramifications that the investigation of allergic disease may take. It is unfortunate, however, that the author does not go more into detail at times; from the practitioner's standpoint this is particularly the case when it comes to treatment. Case protocols would have been desirable, especially in pollen cases, where the treatment recommended differs radically from that generally considered best

by other workers. Some of the clinical observations are so unusual that their incompleteness leaves a critical reader's curiosity unsatisfied. So the reviewer wonders whether Duke means "achylia" or "anacidity" in the twelve of twenty-four cases of perennial allergy subjected to gastric analysis? Was a single examination made or was fractional removal done? What were the detailed neurologic findings in the patient (Case 12) in whom transient and migratory paralysis and anesthesia seemed to be due to allergic reactions?

The observations on reactions to physical agents are very interesting as are the author's theories concerning them. To what extent they are related to hypersensitiveness, and in how far the detailed classification suggested is justified, remains for future more extended observations to determine. The illustrations are very good, except Charts I and II which are on such a tiny scale as to be illegible and useless. R. K.

OUR PRESENT KNOWLEDGE OF HEREDITY. A series of lectures given at the Mayo Foundation and the Universities of Wisconsin, Minnesota, Nebraska, Iowa, and Washington (St. Louis) 1923–1924. Pp. 250; illustrated. Philadelphia and London: W. B. Saunders Company, 1924. Price, $2.50.

THE six lectures of this series, by masters of their subjects, constitute a most up-to-date, scholarly presentation, and yet one that is quite understandable to the ordinary intelligent layman or medico. Castle speaks of the general problem of heredity and its historical setting; McClung of the heredity of sex; Detlefsen, of the inheritance of acquired characters (a problem which is left quite undecided); Maude Slye, of the relation of heredity to cancer; Wells, of the influence of heredity on the occurrence of cancer (without much overlapping on the previous topic); and Guyer on eugenics. We recommend the purchase of the book to anyone interested in the subject. E. K.

A SYSTEM OF CLINICAL MEDICINE. By THOMAS DIXON SAVILL, M.D. (LOND.). Seventh edition. Pp. 1004; 176 illustrations. New York: William Wood & Co., 1925. Price, $9.00.

A SEVENTH edition should be reviewed from the point of view only of its up-to-dateness. The reviewer, therefore, formulated six questions at random before opening the volume. Here are the questions and answers: judge for yourself.

1. Is the van den Bergh test discussed? Yes, both indexed and satisfactorily discussed and method detailed.

2. Are the types of acute leukemia described and differentiated?

Very inadequately; no proper description of cells and no mention of oxydase method of staining.

3. How well is the etiology of infectious jaundice discussed? Quite well.

4. Is the treatment of paresis by malarial inoculation mentioned? Apparently not.

5. How fully is the treatment of diabetic coma with insulin given? Very poorly. The only statement on dosage of insulin in coma may be quoted: "It is safe to give at once 20 to 30 units to an adult in coma."

6. Are allergy and serum sickness described? A good section. Hay fever is, however, blamed on timothy grass alone on page 576 and on the pollen of flowers on page 225.

O. P.

BERGEY'S MANUAL OF DETERMINATIVE BACTERIOLOGY: A KEY FOR THE IDENTIFICATION OF ORGANISMS OF THE CLASS SCHIZOMYCETES. By DAVID H. BERGEY, University of Pennsylvania, assisted by a committee of the Society of American Bacteriologists, FRANCIS C. HARRISON, ROBERT S. BREED, BERNARD W. HAMMER, FRANK M. HUNTOON. Second edition. Pp. 462. Baltimore: Williams & Wilkins Co., 1925.

DURING the two years since the author's *Manual* appeared its usefulness has been amply demonstrated. The second edition is welcomed, not so much for the new species included, but because of the thorough revision which has aided in eliminating errors and in perfecting the classification and nomenclature. The older synonymous names of the different microörganisms are included both in the text and the index, a new feature which greatly facilitates the use of the manual.

J. S.

LECCIONES SOBRE RADIOLOGIA Y FISIOTERAPIA. By FILIBERTO RIVERO, Professor of Radiology and Physiotherapy in the School of Medicine, University of Havana. Pp. 270. Havana, Cuba: Compañia Nacional de Artes Graficas: La Moderna Poesia, 1925.

THE substance of a series of elementary lectures on roentgenology and physiotherapy as presented by the author to his undergraduate medical students. The book gives merely the high points of theory and indications rather than technique, is not illustrated and was written primarily to help the students prepare for examination.

R. K.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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The Recognition of a Biologic Differentiation in the White Blood Cells with Especial Reference to Blood Transfusion.—It has been the observation of the men who frequently give transfusions of blood that in spite of the fact that the red cells and serum of the donor and the recipient match that reactions occasionally occur similar in many respects to the reactions which occur with improperly matched blood. Several different explanations have been given in explanation of this disturbing event. The platelets have shared in the blame for this reaction. The leukocytes have been suggested as one of the formed elements of the blood which might play some part in the production of the usual symptoms that arise after transfusion. CHARLES A. DOAN (*J. Am. Med. Assn.*, 1926, **86**, 1593) brings forth facts to show that in a certain number of cases at least there is a biologic incompatibility of the white cells in blood and the development of hypersensitiveness after repeated transfusions. The observation was made on a series of rabbits. A method was then elaborated to test the compatibility of plasma and white cells. The technique of this method is not particularly difficult and could be readily learned in a short time by laboratory men. By supravital staining it is possible to show that in some individuals their plasma contains a specific leukotoxin which will destroy a goodly number of the leukocytes. The polymorphonuclears are the leukocytes chiefly affected though all the white cells show very distinctive cytoplasmic changes when put in contact with the toxic sera. There is no change in the red cells which are found to be compatible. In view of

the fact that transfusion is frequently not resorted to until an individual is extremely ill, to cause in any such individuals a severe transfusion reaction might result in death. Doan very wisely remarks that the responsibility of a reaction in dangerously weak patients lies with the one who does not make use of every available safeguard.

Symptoms of Coronary Occlusion.—After reviewing the historical facts and the anatomic considerations of this interesting condition of coronary occlusion, LOUIS HAMMAN (*Bull. Johns Hopkins Hosp.*, 1926, **38**, 273) takes up in detail the symptoms, subdividing them into four main groups. The first group of the immediate symptoms associated with the occlusion, the anginal seizure, include pain, shock, suppression of urine with falling blood pressure, all of which are sufficiently characteristic to require no further elaboration. The symptoms (Group 2) associated with myocardial damage, myocardial insufficiency, include dyspnea, of which the author says that with pain and shock, dyspnea makes up the triad that characterize the onset of coronary occlusion. The other symptoms include those of congestive heart failure, Cheyne-Stokes breathing, and the signs of cardiac disturbance. The symptoms (Group 3) associated with the myocardial infarct are the ones that are least frequently accentuated and which are in reality the most important in substantiating the diagnosis. Fever and leukocytosis are invariably present. A friction rub is of extreme importance. The author states that he has rarely heard this important sign—but once in a series of 10 cases. This seems to be contrary to the experience of others. Embolic phenomena are very common and their significance is especially decisive for diagnosis. Cardiac aneurysm with rupture is given as the fourth subhead in this third main head. It is mentioned simply because very occasionally it may cause sudden death soon after the occurrence of the occlusion. The fourth group of symptoms include nausea, vomiting, and diarrhea; the facies; vasomotor phenomena; and nervous symptoms. The discussion of the symptoms is most interesting and it makes up the main portion of the paper. However, the author discusses in the after portion of his manuscript the pathologic anatomy, differential diagnosis, prognosis and treatment.

Advanced Meningococcus Meningitis. Treatment by Combined Ventricular, Cisternal and Lumbar Puncture.—Ayer, Ebaugh and others have shown that cisternal puncture is a procedure which after a certain amount of practical learning of technique is as safe as lumbar puncture and they have shown that such puncture may be of distinct benefit in late severe cases of meningitis. The introduction of specific antimeningococcic serum by lumbar puncture has proven to be a tremendous advance in the treatment of meningitis, but only in the early cases. The serum probably only covers the cord and does not reach the coverings of the brain, or is much diluted or in very weak concentration. This has been proven by the injection of India ink into the lumbar subarachnoid space. On the other hand, cisternal puncture followed by the injection of ink shows that the coverings of the brain and cord are stained with this solution. It has also been shown that failure of the fluid to reach the covering of the brain depends not only upon anatomic difficulties but also pathologic changes produced by the

formation of exudate within the spinal canal which blocks off the entrance of the curative fluid into the head. The ease with which cisternal puncture may be done and the greater value of the method of introducing the fluid will make it seem that it will be the ideal way of treating cases of meningitis. MAX MINOR PEET (*J. Am. Med. Assn.*, 1926, **86**, 1818) reports a case of advanced meningitis in which the patient was treated by ventricular, cisternal and lumbar punctures. This child, aged eight years, had been sick for several days before she was brought to the hospital. A few days after admission, because she had not improved with lumbar puncture, cisternal puncture was performed, and this was done repeatedly until the child eventually recovered. The author feels that without the cisternal puncture the patient would undoubtedly have died. At the Charity Hospital, New Orleans, we have used combined cisternal puncture and lumbar puncture in three patients with pneumococcus meningitis, all of whom died. One patient died very shortly after admission to the hospital, the second patient, although apparently *in extremis* when admitted, survived four or five days after her admission to the hospital apparently as a result of the introduction of a polyvalent pneumococcic serum, while the third patient, in whom an effort was made to gently lavage the meninges and in whom a thick creamy pus came through the lumbar puncture needle, died a few minutes after the withdrawal of the two needles.

Exophthalmic Goiter: A Follow-up Study of Cases Treated with the Roentgen Ray.—Controversy arose when the Roentgen ray was advocated for the treatment of exophthalmic goiter. Surgeons in particular felt that this form of therapy had nothing to recommend it. It would hardly be fair to say that they were activated by selfish motives. However, statistics have been brought forth from time to time, notably by Means and Aub, showing the beneficial effects of radiotherapy. BERTRAM J. SANGER (*Arch. Int. Med.*, 1926, **36**, 627) reports from Columbia University and the Presbyterian Hospital a careful follow-up study of 50 patients who had been under Roentgen therapy. Some of these cases have been followed for as long as five years; 82 per cent of the patients became entirely well and remained so; 6 per cent were improved, 8 per cent were operated on and the fate of the 4 per cent is unknown. It seems from these figures that the conclusions of the author are fair and conservative, namely, that the Roentgen ray offers a safe and satisfactory therapy procedure with a high percentage of cures of cases of exophthalmic goiter.

Experience with Cholecystography in Cases Coming to Operation.—C. C. MCCOY and R. S. GRAHAM (*J. Am. Med. Assn.*, 1926, **86**, 1899) present statistical evidence to show the value of the visualization of the gall bladder by the halogen compounds of phenolphthalein. In 96 per cent of their 26 consecutive cases the cholecystographic diagnoses were confirmed and they believe from their results that this method of diagnosis merits wide application. This report corresponds to the results that others have had and certainly would seem to add additional evidence to the statements already made of the value of the roentgenological diagnosis of disease of the gall bladder.

SURGERY

UNDER THE CHARGE OF

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Abdominal Puncture in the Diagnosis of Acute Intraperitoneal Disease.—NEUHOF and COHEN (*Ann. Surg.*, 1926, **83**, 454) claim that exploratory abdominal puncture is a safe, simple and valuable aid in the diagnosis of obscure acute intraäbdominal disease. It seems to establish the diagnosis of a traumatic or inflammatory intraperitoneal lesion in some cases in which the diagnosis cannot otherwise be made. In other instances abdominal puncture offers conclusive information as to the source and nature of a peritonitis and thus aids directly in arriving at the therapeutic indication as well as the diagnosis. In the peritonitis group abdominal puncture is of especial value in establishing the diagnosis of the pneumococcus and streptococcus infections. Abdominal puncture is contraindicated in any subacute or chronic intra-abdominal disease, in which a loop of intestine may be fixed. A negative abdominal puncture does not exclude the presence of fluid and should therefore never be interpreted as a contraindication to operation in suspected peritonitis or traumatic visceral lesions. Abdominal puncture should be employed as an aid to diagnosis in every obscure acute intraperitoneal lesion, for which operation may be indicated.

Healing of Simple Fractures.—BLAISDELL and COWAIN (*Arch. Surg.*, 1926, **12**, 619) say that age is an important factor in determining certain phenomena that occur at the time of injury and during the process of the healing of fractures. The character of the mechanism of production determines and imparts certain characteristics to each fracture according to age and environmental conditions attending each injury. The bones of young animals yield to force by bending, buckling on the side of angulation from compressive stress or fracturing on the side of tensile stress (true greenstick). The property of yielding to bending stress diminishes as age advances, as the result of increased deposition of earthy salts in the bones. The bones of adults when normal and subjected to stress, yield by sudden solution of continuity with resulting molecular shock, accompanied by more or less fragmentation. The periosteum is more or less lacerated and loosened from the surface of the diaphyseal cortex. By compressive stress the bone cells are destroyed for a variable distance from the line of fracture. This injury is recognized by the irregularly distributed areas of empty lacunæ in the cortex of the diaphysis. Bone cells in the immediate vicinity of the fracture line are always destroyed and the ruptured bloodvessels are closed by bloodclot. Cartilage, fibrocartilage and osteoid tissue not permeated by earthy salts are removed mainly by vascular erosion. After earthy salts have been

deposited in osteoid tissue, osteoclastic action is called for. Osteoclasts by the formation of Howship's lacunæ roughen the surface of the diaphyseal cortex and that of fragments preparatory to the deposition of fibrous and osteoid callus. The deposition of fibrous or osteoid callus on the surface of the cortical bone so roughened secures firm interlocking or attachment between the old and new bone. Bending stress when applied to healing fractures may bring about separation between the new bone and the old cortex. When the periosteum is lacerated and the edges retracted it allows the ingrowth of fibrous tissue from the outer layer. This tissue is not osteogenetic and it forms a barrier to osseous union of the fragments. Cartilaginous callus usually does not appear within the medullary callus. This sometimes occurs, however, as the result of the ingrowth of subperiosteal elements which possess an inherent tendency to develop chondroblasts. This ingrowth is apt to follow in cases of comminution, in which proper alignment is difficult or impossible. Callus formation between the cortical ends of the major fragments is the last to take place. The interval is often filled from within and from without.

Synovectomy in Chronic Infectious Arthritis.—SWEET (*Am. J. Surg.*, 1926, **40**, 49) states that Jones recommends synovectomy for quiescent cases of monarthritis of the hypertrophic type urging care to avoid interfering in progressive disease. Speed recommends synovectomy as a valuable procedure in properly selected cases, as it allows us to restore function to joints for which otherwise little can be done. Monarticular lesions offer much the best prognosis. He says synovectomy during the progressive stage of polyarticular arthritis is of doubtful value as a routine procedure. The writer believes that synovectomy is an operation that warrants further trial in carefully selected cases of chronic infectious arthritis. It may be expected to promote the restoration of function to those joints in which resolution of the exudate has been delayed. It may also prevent the further destruction of the cartilages and the secondary ankylosis which would result from the prolonged presence of large amounts of organized inflammatory exudate. This operation is applicable to those joints in chronic infectious arthritis in which there is delayed resolution of the synovial exudate. It should be done before bone and cartilage changes occur in hope of preventing such changes. Bone and cartilage changes, however, do not contraindicate synovectomy, but the resultant benefit may be prejudiced by such changes and to a degree in direct proportion of their extent.

PEDIATRICS

UNDER THE CHARGE OF

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The Prevention of Rickets.—WILSON (*Am. J. Dis. Child.*, 1926, **31**, 603) found that in children from one to three months of age, born in

the spring and summer of 1924 who received graduated doses of ½ to 1½ teaspoonfuls of a biologically tested cod-liver oil showed development of clinical rickets in 91 per cent of the subjects. A more comprehensive study of 47 infants beginning at the age of two weeks who were born in the winter of 1925, and who received daily doses of 1, 2, and 3 teaspoonfuls of biologically tested cod-liver oil showed a development of clinical rickets in 68 per cent of the cases as compared with 76 per cent of a controlled series of 30 cases. She found that 97 per cent of the infants born in the summer and 91 per cent of infants born in the winter, who received cod-liver oil, showed Roentgen ray evidence of rickets. She also found that 97 per cent of the infants born in the summer and 98 per cent of the infants born in the winter who did not receive cod-liver oil showed Roentgen ray evidence of rickets. Rickets was observed earlier by Roentgen ray than by clinical examination, being observed in 4 per cent at one month of age compared with a total of 4 per cent at two months by clinical examination alone. By the fourth month rickets was present in the majority of infants in both groups. The early age incidence of the development of rickets in this series indicates the necessity for measures of prevention or control to be started in the first month, particularly for children born in the winter. The correlation of the clinical and Roentgen ray evidences of rickets observed at the various age periods in this study indicated that active rickets is encountered most frequently in the first six months of life and healing rickets after six months. There did not seem to be any relation between the degree of rickets observed and the amount of cod-liver oil received. Concentration of calcium and inorganic phosphorus in the blood serum of the infants under five months of age with early clinical and Roentgen ray evidence of the disease, was found to be within the normal range. A comparison of the degrees and incidence of rickets observed in infants receiving and infants not receiving cod-liver oil did not show any striking difference. Infants receiving cod-liver oil showed rickets that healed earlier than that of the controlled series. Judging from the data obtained in this study it would seem that the cod-liver oil therapy was more a matter of control than of prevention.

Goiter in Children in New York City.—Cohen (*Am. J. Dis. Child.*, 1926, **31**, 676) presents the results of a survey of 1184 school girls and 783 school boys. It was found that the incidence of simple goiter in school children and in an older group of women, as well as investigations into the conditions of iodin intake which determined endemic centers of goiter do not justify the conclusion that New York City is an endemic center of goiter. The mild sporadic cases of simple goiter which occur among school children seem to depend on the relative insufficiency of iodin due mainly in the physiologic cause, puberty. In New York City thyroid enlargement occurred three times more frequently in girls than in boys. Simple goiter among the children in New York reached its puberty between the ages of thirteen and fifteen years in both sexes. The percentage of incidence of normal glands seemed to vary inversely with the degree of activity of menstrual cycle. The mild cases of simple adolescent goiter observed among the school children of this city showed in the case of the girls a distinct tendency to spontaneous regression after puberty and in the boys there was a complete

regression. The author recommends the following as a public health measure, that physicians in nongoitrous centers be impressed with the importance of regarding simple goiter as a symptom of relative or absolute deficiency of iodin in the thyroid gland and of undertaking its prevention, early recognition and care, especially during adolescence and pregnancy. That they consider the advisability of administering very small doses of iodin regularly to pregnant women and thus possibly diminish the tendency to goiter at puberty. That the medical service, especially in high schools, but also in colleges, teachers' training schools and elementary schools, include an examination and notation of the condition of the thyroid gland. That cases of thyroid enlargement be reported to parents with instructions to seek medical advice. That parents be informed that simple goiter can be prevented and cured, especially in the early stages of development, by minute doses of iodin. That they be impressed with the importance of preventing and curing simple goiter, especially during adolescence and pregnancy and that they be encouraged to seek periodically medical advice for their children and themselves.

Properties of Some Fabrics Used in Infants' Underwear.—FABER and HADDEN (*Arch. Pediat.*, 1926, **43**, 283) made studies of materials frequently used for infants' underwear and they found that of the four materials used for undershirts for babies, cotton appeared to be superior in practically all important respects. Contrary to the usual belief, it appears to be definitely warmer than wool weight for weight. Silk is only slightly less warm than wool. As an absorbent wool appears to be unsuitable material since it is wet with difficulty and tends to keep unabsorbed perspiration for a long time in contact with the skin. This is probably the reason, or one of the chief reasons why wool is distinctly uncomfortable and causes itching. More important than the discomfort is the likelihood that the failure of wool to absorb moisture tends to cause slight maceration of the skin and increases the chances of infection. These chances are much increased by the fact, which is well known to every housewife, that wool must be washed only in lukewarm water and with a minimum of handling since it will readily shrink and otherwise deteriorate. Cotton, however, can be thoroughly washed and even boiled without undergoing rapid damage. All fabrics, especially knitted ones, retain large numbers of bacteria, even after repeated rinsings and a high degree of cleanliness such as is necessary in infants' clothing can only be obtained by boiling. In this regard silk shares the disadvantage with wool which is only partly offset by the fact that it is, more than other materials, freed of bacterial soilure by repeated rinsing. In other respects it is only a slightly poorer heat insulator than wool and it absorbs moisture very much faster. Linen mesh is the poorest heat insulator of the four and it wets less well than either cotton or silk but much better than wool. It will withstand boiling without great damage. This material may be a fairly suitable one for very warm weather but even then it is probably not as good as a light weight cotton knit material with a very open mesh. Of the two diaper materials commonly used Birdseye is probably better than Canton flannel, although the latter has a somewhat greater total capacity for water.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Creeping Eruption.—J. L. KIRBY-SMITH, W. E. DOVE and G. F. WHITE (*Arch. Dermat. and Syph.*, 1926, **13**, 137) believe that a parasite, Agamonematodum migrans, is the cause of creeping eruption in the Southeastern United States. They found this microscopic nematode parasite in larval state in 5 patients out of 50 examined by taking serial sections. It is $\frac{1}{50}$ of an inch in length and $\frac{1}{1200}$ of an inch in breadth. All these patients had multiple lesions. This is the first recovery of this nematode from lesions of creeping eruption; although nematode larvæ of the genus Gnathostoma have caused a group of creeping diseases, while insect larvæ have invaded the skin to cause another group. In over 2500 cases of creeping eruption reviewed, it has been observed on every part of the body, and most often on the feet. It is usually characterized by a linear, tortuous, and serpiginous eruption caused by the migrations of the parasite and accompanied by intense itching. The infection occurs more often in children than in adults and is most frequent during the summer, following rainy weather. Various animals have been mentioned as possible hosts, but the origin of some cases in rat-infested places, lays suspicion on this animal. The authors have found that ethyl acetate applied on cotton or gauze or used in a flexible collodion is an effective treatment in many cases; on others, refrigeration with ethyl chlorid or carbon dioxid snow was successfully used.

Histopathology of Syphilitic Hypoplasia of the Teeth.—LOUIS J. KARNOSH (*Arch. Dermat. and Syph.*, 1926, **13**, 25) studied the dental stigmas of hereditary syphilis and concludes that they are developmental deformities. The true Hutchinsonian incisor is a deformity of the developmental lobes of the permanent central incisor and not one of a transitory calcium deficiency; it shows no distinct cross striations, but it can be modified by concurrent nutritional disturbances. The true mulberry molar of syphilis is a first permanent molar characterized by enamel cusps showing crests of sound enamel on a base of hypoplastic formations; these cusps are generally crowded together on a crown surface of dwarfed dimensions. The tubercle of pseudocusp of Carabelli on the mulberry molar of syphilis is formed by the buckling or telescoping of normal enamel layers over dwarfed and hypoplastic formations. In a true sense this structure is not a supernumerary cusp, because it possesses no underlying dental cap. The true supernumerary cusp which generally lies on the lingual aspect of this molar, and which is regarded by the average dentist as an anomaly of no special signifi-

cance, should not be confounded with the tubercle of hypoplasia. The latter lies, generally, below the level of the normal cusps at the junction of the hypoplastic and normal portions of the crown. It is a feature, consequently, of any severe hypoplasia of the molar in which the first year layers are dwarfed and grossly deficient. In the first dentition, congenital syphilis produces characteristic changes only in the second deciduous molar; this consists of a pitting across the crown and generally proximal to the occlusal surface. The author believes that the time factor as a cause of dental hypoplasia seems to be established in the first year of life, the effects coming on suddenly at birth, and occur with the stomatitis, rhinitis and the other familiar symptoms of the newborn. This is in direct contrast with the opinion previously held that the intoxication acted previous to birth.

Curative Effect of Bismuth Compounds in Experimental Rabbit Syphilis.—An extensive study of experimental syphilis in the rabbit was conducted by G. W. Raiziss and M. Severac (*Arch. Dermat. and Syph.*, 1925, **12**, 661) in an effort to evaluate compounds of bismuth as compared with those of arsenic and mercury, some of the experiments continuing for more than eight months. On the basis of observations and the method of popliteal node transfer, it was found that bismuth compounds are sufficiently curative to cause complete eradication of syphilitic infection in rabbits. The authors conclude that arsphenamin derivatives are still the basic remedies in the treatment of syphilis; bismuth compounds (injected intramuscularly) are next; the latter being distinctly superior to mercury.

Clinical Study of Kahn Precipitation Test and Kolmer Complement-fixation Test.—R. L. Kelly (*Arch. Dermat. and Syph.*, 1925, **12**, 720) performed a Kahn precipitation test and a Kolmer complement-fixation on the serums of 110 cases. The precipitation test was performed according to the method advised by Kahn, except that inactivation was carried on for only fifteen minutes and that the readings were checked the following morning after ice-box incubation; the doubtful and weaker reactions becoming more distinct in this way. Concordance of results was found in 94.5 per cent or 105 cases. In the five conflicting results, 4 of the patients were know to have had syphilis, and the other case was clinically suggestive; one of the 4 known cases failed to give a positive reaction to Kahn and then to the Kolmer; all 5 gave a positive Kolmer, however, when the natural antisheep hemolysin was removed. The author feels that there is a remarkable degree of harmony between the 2 cases; that a high degree of sensitivity and specificity are common to both; and that it is well to perform both tests in doubtful cases.

Value of Nonspecific Therapy in Syphilis.—S. S. Greenbaum and C. S. Wright (*Arch. Dermat. and Syph.*, 1925, **12**, 858). The effect of nonspecific therapy (injections of a 4 per cent suspension of milk protein intramuscularly) was studied on 25 cases of latent syphilis which were being treated by neoarsphenamin intravenously. For comparison, 25 patients with latent syphilis, who were being treated by neoarsphenamin alone, were studied at the same time. In secondary and tertiary cutaneous syphilids, nonspecific therapy alone had had a favorable

influence; thus suggesting that perhaps the effect of the injections was to stimulate the natural protective forces of the body. The authors found 68 per cent became seronegative with the combined treatment, as compared with 48 per cent under neoarsphenamin alone. Furthermore, 52 per cent of those receiving combined treatment remained persistently negative; whereas only 20 per cent remained so with neoarsphenamin alone. It is concluded that nonspecific protein therapy may prove a valuable adjunct to the usual antisyphilitic remedies.

OBSTETRICS

UNDER THE CHARGE OF

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Says Maternity Bill Will Make a Midwife Out of Uncle Sam.—(*Chicago Tribune Press Service*) (*Illinois Med. J.*, 1926, **49**, 185). Representative Tucker (Dem., Va.) took exception to the allowance of the $1,000,000 for hygienic, maternity and infancy work under the Sheppard-Towner Maternity Act, as proposed in the pending department of labor. The Democratic Representative from Virginia is of the opinion that this will make Uncle Sam the midwife for every expectant mother in the country and a wet nurse for its babies. He considers this government aid, as state socialism and is against the government appropriating any money to any function which properly belongs to the individual states.

A Clinical Study of Nephritis in Cases of Pregnancy.—Rockwood, Mussey and Keith (*Surg., Gynec. and Obst.*, 1926, **42**, 342) take up the clinical study of nephritis and the types found and tabulated with the end results of patients which were pregnant and showed some definite kidney disease. They show that the ideas of the obstetrician and the internist are frequently at variance, as they do not use the same tests in searching for abnormalities of metabolism. Frequently patients dismissed by the obstetrician appear later in the consulting room of the internist with definite nephritis. On the other hand, a patient may assure the internist that she had a very severe toxemia during pregnancy although there is no signs of residual damage. The cases studied included those who showed signs of hypertension, edema or renal injury during their present pregnancy, and were classified on the basis of Volhard and Fahr. Acute glomerulonephritis, acute nephrosis, acute nephritis, chronic focal nephritis, benign hypertension

and malignant hypertension are discussed and include case history, follow-up records, with full blood pressure, urinary findings, renal functions and occular examinations, with blood chemistry studies under each type of classification. The summary shows that many toxemias of pregnancy are associated with nephritis, and can be classified as are other types of nephritis, not necessarily occurring in pregnancy. Both nephritis and toxemia of pregnancy seem to be general diseases affecting the cardiorenal vascular system, as a whole. When the toxemias of pregnancy are classified by the same method which Volhard uses for nephritis, a marked difference in end results is seen, and this difference allows the physician to make a more accurate prognosis both as to the mortality among the mothers and the fate of the child in subsequent pregnancies.

Shock in the Pregnant and Puerperal Woman.—Harold Bailey and Wm. P. Driscoll (*Am. J. Obst. and Gynec.*, 1926, **11**, 287) report 3 cases of maternal deaths in a series of 2323 deliveries and 37 per cent of the deaths in a series of 1477 deliveries due to shock, are discussed. Treatment is outlined, strangely advocating the use of 300 cc. of 6 per cent gum acacia in 20 per cent glucose solution injected intravenously at the rate of 3 to 4 cc. per minute at a temperature of 140° in all cases where shock is complete and the blood pressure is 80 mm. or below. This is followed as soon as feasible by blood transfusion in cases where blood loss has been excessive.

The Use of the Vaginal Stethoscope in the Early Diagnosis of Pregnancy.—F. H. Falls (*Am. J. Obst. and Gynec.*, 1926, **11**, 309) has devised a stethoscope which can be applied through the vagina against the lower uterine segment, with the patient in the Fowler position, fetal heart sounds and fetal motion can be heard from the fourteenth to the sixteenth week up to the twentieth week, at a time when they are not heard by abdominal examination. The early diagnosis and differential diagnosis of pregnancy is thus facilitated. Its application in placenta previa is being studied.

The Incompatibility of Pregnancy and Fibroids of the Uterus.—G. C. Mosher (*Am. J. Obst. and Gynec.*, 1926, **11**) stresses the fact that there is such an incompatibility as demonstrated in the frequency of sterility associated with fibroids, the tendency to abortion and premature labor in these patients and the possibility of complication in the pregnancy owing to obstruction at the brim of the pelvis, to pain, to hemorrhage and to sepsis. The vast majority of cases are not recognized as no pronounced symptoms are presented. If the tumors cause dystocia, myomectomy or hysterectomy should be considered. Abortion is not to be considered as an expedient in case of a pregnancy so complicated on account of risk of hemorrhage, traumatic injury or septic infection. The great majority of cases run a favorable course after the immediate danger of postpartem hemorrhage.

Puerperal Sepsis.—(*Can. Med. Assn. J.*, 1926, **16**, 198). Discussed by the Royal Society of Medicine, Section of Obstetrics and Gynecology. The rational form of treatment advocated was to increase drainage by promoting a flow of lymph through the uterus. This was accomplished

by filling the uterine cavity with glycerin through a catheter, this is repeated once or twice a day. Intravenous injections of novarsenobillon and transfusion of immunized blood is advised in septicemia. Hemolytic streptococcus is given as the infecting organism in over 90 per cent of cases of septicemia. Virulence of the infection can be judged by the number of organisms per cubic centimeter of blood, more than 100 being fatal.

Abortion of One Twin, Delivery of Second at Term.—M. G. Burris (*Can. Med. Assn. J.*, 1926, **16**, 170) reports a case occurring in a multipara (3) who aborted a 3 inch fetus on April 30, 1925, and delivered normally on November 4, 1925, a full-term living child. Pelvic examination was entirely normal after the puerperium.

The Toxemias of Pregnancy from the Viewpoint of Etiology.—E. K. Maclellan (*Can. Med. Assn. J.*, 1926, **16**, 292). In this article the question of the etiology of toxemias of pregnancy, and the particular theories relative to the toxemia, being of chorionic origin, and the question of the absence of consanguinity between the mother and fetus is discussed. The author states that the experimental work done has failed to reveal any evidence which would indicate that a diseased state of the chorion exists in toxic cases. The theory of absence of consanguinity has recently been investigated by Zotterman and Wildner in a series of 213 cases in which it was found that incompatibility existed in 26.9 per cent. McQuarrie found 70 per cent incompatible in a series of toxic cases as opposed to 11. 4 per cent incompatible among his normal cases. C. O. Maland states (although data submitted is not sufficient to warrant the drawing of final conclusions, they are suggestive of the relationship between the incompatibility of maternal and fetal blood on one hand, and the development of eclampsia or preëclamptic toxemia on the other).

Maternity and Infancy Work in Pennsylvania.—Editorial. (*Atlantic Med. J.*, 1926, **29**, 469.) Bills are now before Congress relating to the extension of the Sheppard-Towner appropriation for maternity and infancy work. In 1925 under the administration of this fund there were 290,590 children given complete physical examinations; 10,800 Child-Health Conferences held; and 3581 Prenatal Conferences attended by 36,000 women. There were established 622 new Child-Health Centers and 57 Prenatal Clinics. The United States is expending at present less than $1,000,000 per year in subsidies to the States for promotion of a health program for Mothers and Babies. Statistics showed in 1924 a substantial drop in the infant death rate, which, however, is still comparatively high. Since 1922, Pennsylvania has been receiving a Federal Appropriation of $69,000 annually as provided in the Sheppard-Towner Bill. All but $5000 of the appropriation had to be matched with State funds. This fund has been expended in conducting Child-Health Conferences, Prenatal Work, Supervision of the Midwives and quantities of literature on the care of children, hygiene of pregnancy and dental and mental hygiene; Special "Campaigns" exhibits and public health nurses have been supported by this special appropriation. Pennsylvania has reduced the infant death rate from 167 per thousand living births in 1906 to 78 per thousand in 1924.

GYNECOLOGY

UNDER THE CHARGE OF

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Irradiation of Cervical Cancer.—At the Mayo Clinic, BOWING (*Am. J. Obst. and Gynec.*, 1926, **11**, 400) states that the cases of cancer of the cervix are classified entirely according to the location and extent of the disease. In Group 1 are cases with early or operable lesions in the cervical canal. In Group 2 are included the borderline cases with disease limited to the vaginal face of the cervix. In Group 3 are the inoperable cases. A case is considerable inoperable when the disease has extended to the vaginal walls, broad ligaments, pelvic lymph nodes, and so forth, and usually with some degree of fixation. In Group 4 are the recurring cases. One should be reasonably sure the original lesion was operable, and the skill of the operator must be beyond question. Group 5 includes all cases in which the procedure was incomplete and only modified the lesion, such as complete operation, one or more applications of the actual cautery, and insufficient radium and so forth. This is designated the modified group. In Group 1 dilatation and curettage are usually necessary to make a definite diagnosis since the disease is beyond the vaginal face of the cervix. Should the material removed be reported malignant by the pathologist, total abdominal hysterectomy is performed immediately. Radium and Roentgen ray therapy must be considered as a postoperative procedure; its use depends on the findings of the surgeon and the pathologist. Should a tumor of Group 1 or 2 be confined to the superficial tissue of the cervical canal and be entirely removed by the surgeon, the advisability of irradiation as a postoperative procedure is questionable. Should it prove to be a tumor of Group 3 or 4 with involvement of the deeper tissues of the cervical canal, radium and Roentgen ray therapy as a postoperative procedure is indicated. At least two applications of radium to the vaginal stump should be given, using a vaginal applicator of sufficient size to contain the universal silver radium tube, with walls of 1 mm. brass and 3 mm. hard rubber. The radium is allowed to remain in position for a period of from ten to fourteen hours at each application; this is supplanted by Roentgen ray therapy to the lower abdomen, back, and lateral walls. A careful follow-up should be instituted for a period of from eighteen to twenty-four months. He recommends three or four cervical applications of radium for periods of from twelve to fourteen hours each, giving about two treatments a week. At the end of the series, from six to eight weeks should elapse to allow the cervix to heal, although in certain cases a few weeks more may be necessary for com-

plete healing. At this time total abdominal hysterectomy should be considered. In a small group of cases so treated, no active carcinoma could be found by the pathologist in the specimens removed. One surgeon volunteered the information that the operation was easily performed; there was but little tissue ooze, and the fascia planes separated easily. But to ensure satisfactory tissue changes, it is necessary that a sufficient interval elapse between the first application and the operation. This is usually in terms of weeks rather than days. As a prophylactic procedure, radium and Roentgen ray therapy should be given as outlined for Group 1 and with the same follow-up observations. For Group 3 radium and Roentgen ray treatment is given. Owing to the extent of the lesion, regardless of the improvement that may occur, surgical treatment in this group will not improve the end results. For purposes of radiotherapy, this group should be divided into two classes: One in which the general condition is good and the other in which the general condition has been undermined by the disease. In the first of these well-planned and applied doses of radium, a total of about 3000 mg. hours for each 2.5 cm. depth of involved tissue by the broken-dose method, should be given. The Universal silver tube applicator containing 50 mg. of radium element (sulphate) is used for periods of from fourteen to twenty hours each and applied about twice a week. Two or three treatments, employing the vaginal applicator, are also used, supplemented by a course of Roentgen ray treatment as outlined for Groups 1 and 2. Marked palliation should follow. The rule is that this treatment is never repeated; it is therefore important that the first series of treatments be sufficient. A follow-up course, as for Groups 1 and 2, is also necessary. When the health is undermined, the disease is usually widespread and radium treatment should be given cautiously. A total of from 1500 to 3000 mg. hours is employed, the applicator being inserted into the substance of the tumor or crater. A course of Roentgen ray treatment as previously mentioned should also be given. As a rule, further radium treatments are contraindicated. Groups 4 and 5 may be considered together. The amount and location of the infiltrating tumors make it impossible to outline a course of treatment. In these he employes various types of radium applicators such as the, Universal silver tube containing 50 mg. of radium element (sulphate) steel alloy needles, containing from 5 to 10 mg. of radium element (sulphate) each, platinum iridium needles containing 1 mg. of radium element (sulphate), or seeds containing emanation (Radon) less than 1 millicurie each. These are buried into the substance of the tumor about 1 cm. apart, in an attempt to get equal distribution of the energy throughout the tumor. The vaginal package is used to radiate the apparently uninvolved vaginal wall. In Group 4, much depends on the extent of the lesion at the time of treatment, and it is astonishing how much palliation may occur.

Ureteral Drainage after Operations for Vesico-vaginal Fistula.—Every surgeon who has to deal with cases of vesicovaginal fistula realizes that in order to get a good result after any of the recognized operative procedures it is important that the bladder be kept as much at rest as possible for a few days, and for this purpose such procedures as the retention catheter, the suction catheter or suprapubic bladder drainage has been employed by different operators. A new method of

keeping the bladder at rest which consists of the use of the ureteral catheter has been suggested by FUCHS (*Zent. f. Gyn.*, 1926, **50**, 868). In the case which he describes there was a large vesicovaginal fistula through which the bladder wall prolapsed into the vagina. This opening was situated in the region of the trigone and on each side of the opening the ureteral orifices were situated and discharging urine. It was apparent that even if the bladder defect were carefully closed that the peristaltic action of the ureters would be detrimental to the proper healing and the continuous passage of urine over the wound might be a factor in the recurrence of the condition. For this reason, he inserted catheters into each ureter and led them out through the urethra before repairing the fistula. After the operation the ends of the catheters were placed in a 10 per cent formalin solution and every hour a small amount of boric acid solution was syringed through the catheters in order to be certain that there were patulous. At the end of sixteen hours the catheters were removed and both were found to be patulous while the bladder itself was perfectly dry. A Pezzer catheter was then inserted into the bladder and allowed to remain for eight days after which the bladder was catheterized at short intervals for a further period. The result of the operation was perfectly satisfactory in every way and Fuchs feels that for difficult cases of vesicovaginal fistula especially in the neighborhood of the ureter that bilateral ureteral drainage is an improvement over the previous types of bladder drainage because it practically prevents the sphinteric contractions of the ureteral orifice and, furthermore, it is practically the smallest foreign body with which the bladder can be kept completely dry.

Pelvic Inflammatory Disease.—In an analysis of 1105 cases of pelvic infections in the Harlem Hospital of New York City, CHERRY (*Surg., Gynec. and Obst.*, 1926, **42**, 600) found that the gonococcus is the inciting agent in 88 per cent of the cases. He believes that exclusively conservative treatment of adnexal disease is, on the whole, unsatisfactory. The patient upon discharge from the hospital is inclined to ignore the advice given urging return visits, and reinfection of the adnexa often occurs. Injections of foreign protein in the form of milk preparations (aolan) and horse serum have proved unsatisfactory. The use of diathermy as a conservative measure in the treatment of adnexal disease of gonorrheal origin was the most successful of the palliative methods, as it caused a resolution of pelvic masses in 66.6 per cent of patients, besides relieving pain in practially 100 per cent. It also, by proper application of electrodes, controlled the infection of the lower genital tract. Initial acute attacks of adnexal inflammation should not be treated surgically, as they spontaneously subside. Reinfection should not occur if the lower genital tract is properly treated. Recurrent attacks of pelvic inflammation are excellent reasons for the surgical removal of the pelvic lesions. Such surgical procedures can be performed with a reasonable assurance of not more than a 3 per cent operative mortality, if the temperature has remained normal for three to ten days and the leukocyte count is below 16,000. When in the course of operative removal of infected adnexa, pus contaminates the peritoneal cavity, the best results as to mortality and wound union are obtained by closure of the abdomen without drainage. If drainage is necessary the vaginal route is better than the abdominal.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Bacterial Flora of Nose and Throat in Health and Upper Respiratory Infection.—"In searching for the causative agent in respiratory disease the problem is seriously complicated by the fact that the nose and throat normally harbor a variety of bacteria, some constantly present and others more or less transient. Correct interpretation, therefore, of the importance of organisms found in respiratory disease is dependent upon comprehensive familiarity with the bacterial flora in health." As a preliminary investigation of the Common Cold, SHIBLEY, HANGER, and DOCHEZ with the assistance of MILLS (*Proc. Soc. Exper. Biol. and Med.*, 1926, **22**, 258) studied the bacterial flora of the nose and throat of 13 individuals for periods ranging from five to nine months. Aërobic and anaërobic cultures were made from the nose and throat infections weekly in health, and daily in the course of colds and throat infections. The normal basic nasal flora included Staphylococcus albus, diphtheroids, and for certain persons, Staphylococcus aureus and citreus; occasional transients were Gram-negative cocci and nonhemolytic streptococci. The normal basic throat flora included Gram-negative cocci, nonhemolytic streptococci, and for certain individuals large Gram-positive cocci, B. pfeifferi, and diphtheroids; transients were Staphylococcus albus, Staphylococcus aureus, hemolytic streptococci, Staphylococcus citreus and pneumococci. Certain socalled potential pathogens, such as hemolytic streptococci, Staphylococcus aureus, pneumococci and B. pfeifferi, were found both in the presence and absence of demonstrable untoward symptoms. In the course of colds a number of changes from the normal were voted. In the nose there was a tendency toward scantiness of growth in the early cultures and the basic flora was decreased; in the throat the usual prominence of Gram-negative cocci was less marked and there was a moderate increase in the prominence of nonhemolytic streptococci. In the nose hemolytic streptococci and B. pfeifferi showed increases which were due entirely to late secondary spread. In the throat Staphylococcus aureus, hemolytic streptococci and B. pfeifferi went up; in the case of the two former this was due to secondary spread. The increase of B. pfeifferi was due mainly to the fact that the organism was widespread, in normals as well, at the time of the investigation (late winter and spring). No bacteria were found in the first or in early cultures to which an etiologic rôle could be attributed. The authors believe that the socalled pathogens to which they have referred probably play a secondary rôle in the type of upper respiratory infection under investigation. Cultures taken during sore throats showed the expected increase, in the throat, of hemolytic streptococci (from 17 per cent in normals to 56 per cent during infections).

The Nasal Passages in Lobar Pneumonia. A Clinical and Bacteriological Study.—The frequency of pneumococcal infection of the paranasal cavities in lobar pneumonia was noted by Darling, when he demonstrated, at autopsy, acute inflammatory changes in one or more nasal sinuses in more than 90 per cent of a series of pneumonia cases. As no data referable to clinical observations of the nasopharynx in pneumonia were found, FELTY and HEATLEY (*J. Am. Med. Assn.*, 1926, **86**, 1195) performed bacteriologic examinations from the nasopharynges of 16 persons with lobar pneumonia. The cultures were taken by means of a swab applied to the middle meatus of each side of the nose. The material was injected into the peritoneal cavity of a mouse, and in certain cases cultures were grown on rabbits' blood-agar plates. The pneumococci were typed by agglutination, as were the pneumococci isolated from the sputum by the same method. Cultures, similarly procured from 11 patients who were not suffering from pneumonia at the time, and used as controls, yielded no pneumococci in 9 instances. From the other 2, pneumococci (Type IV) was obtained; these patients had had a previous attack of pneumonia caused by a pneumococcus of another type. Of the 16 cases with lobar pneumonia, pneumococci of corresponding types to those found in the sputum were isolated from the middle fossæ of the nose in every case. The nasal passages in 15 of these cases were examined with the nasopharyngoscope; of these, all showed hyperemia of the mucosa and 6 had signs of acute suppurative sinusitis. In 8 cases anteroposterior roentgenograms of the sinuses were made, in 7 of which clouding of one or more of the sinuses were observed. The authors discuss various other etiological and clinical phases of their subject and conclude by saying that "the series of cases here reported is too small to warrant the drawing of definite conclusions. The results are sufficiently striking, however, to encourage further investigation of this phase of the disease."

Hyperthyroidism — Its Significance in Otolaryngology. — WAUGH (*Ann. Otol., Rhinol. and Laryngol.*, 1926, **35**, 152) after a comprehensive dissertation on the various aspects of "hyperthyroidism," concludes from his observations at the Cleveland Clinic: (1) That the relation of infection to hyperthyroidism is not definitely known; and the removal of a focal infection is not a cure for the hyperthyroidism; (2) that under ordinary circumstances, and particularly in children, the surgical removal of a focus of infection should be deferred until the hyperthyroidism has been controlled by surgical treatment; (3) that a sudden death during an operation upon the throat, which is often attributed to the anesthetic or to cardiac failure, may be due to the presence of unrecognized hyperthyroidism; (4) that throughout the entire conduct of a case of hyperthyroidism unusual preoperative and postoperative precautions are essential; and (5) that when it is imperative that an operation be performed in the presence of hyperthyroidism, the presence of the internist at the operation and his coöperation during the period of convalescence is of the utmost importance. The author also calls attention to the fact that in children the presence "of a thymus gland often associated with hyperthyroidism may add materially to the operative risk."

RADIOLOGY

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A Clinical Study of Cholecystitis with the Aid of Cholecystography.—In cholecystography we have a method that will give reliable information in early cholecystitis and as interpretive acumen increases this will be more readily recognized. ZINK (*Radiology*, 1925, **6**, 286) thinks that it is only a question of time until the full potentialities are recognized and developed. The two methods of dye administration now chiefly employed are oral and intravenous. The latter is the method of choice in cases not presenting any of the following contraindications: (1) Obstruction of the common duct; (2) extensive hepatic destruction; (3) hypertension; (4) cardiac disease, especially auricular fibrillation, or cases in which there is myocardial damage, and (5) hyperthyroidism. He quotes various objections to the oral method; the method should be relied upon only in cases presenting (1) normal shadow; (2) stones; negative or positive shadows, and (3) topographical defects. Questionable findings following oral administration should be checked with the intravenous method. In 150 oral administrations 10 per cent were nauseated and vomited; about 25 per cent had mild epigastric discomfort, lumbar pain and mild diarrhea. Their experience in 513 cases with intravenous method did not substantiate the objective held by many workers, since the use of the sodium salt of tetraiodophenolphthalein entirely there were no reactions of importance and no local tissue changes. The diagnosis of gall-bladder disease by cholecystography is dependent upon: (1) Excretion by the liver; (2) patency of the cystic duct, and (3) mucosal concentrating ability of the gall bladder, which is largely dependent upon the condition of the regional lymphatics. Failure to secure a shadow indicates: (1) Cystic-duct occlusion; (2) hepatic insufficiency; (3) small sclerotic gall bladder with obliterated lumen; (4) cystic-lymphatic damage, and (5) failure of dye absorption (when given orally). The bodily type influence gall-bladder motility; the time of appearance of the best shadow is of more importance. Experimental work would seem to concede the emptying of the gall bladder to take place *via* the cystic duct. With the older methods the diagnosis of gall stones was practically limited to those having a sufficient calcium content to be opaque, the use of the dye has added the negative stone shadow, visualized in one of two ways: (1) production of a mottled appearance throughout the gall-bladder shadow; (2) peripheral absorption of the dye by the stones, producing a calcified ring with a negative center.

Cholecystography by the Oral Method.—LEVYN and AARON call attention to the fact (*J. Rad.*, 1926, **6**, 204) that ordinary gelatin capsules are rapidly dissolved in the stomach and the soluble tetraiodophenolphthalein is converted into an insoluble white sediment by the action of hydrochloric acid. In their series of cases, untreated double capsules were used, the inner capsule containing the dye and the outer being filled with sodium bicarbonate. By this means of administration it was found that a greater number of gall bladders were visualized, fewer capsules passed through the intestine undigested and a greater amount of the dye was absorbed. By way of preparation the patient was given 1 or 2 ounces of castor oil two nights before administering the dye. He was given a liquid diet one day previous to the examination and the capsules, each containing 0.25 gm. of the iodin salt, were given every half hour beginning one hour after supper, which consisted of cereal, toast and tea. Twelve capsules were given to patients weighing up to 150 pounds, 15 up to 164 pounds, and 18 up to 200 pounds. A glass full of water containing 2 gm. of sodium bicarbonate was given at frequent intervals during the ingestion of the capsules. The gall bladder was demonstrated in 85 per cent of the cases.

Gall-bladder Diagnosis from the Standpoint of the Surgeon.—The frequency of disease of the gall bladder is now attested by the fact that it constitutes the most common organic cause of dyspepsia and the importance of accurate methods of diagnosis is therefore obvious states GRAHAM (*Radiology*, 1925, **6**, 273). That hepatitis is a constant accompaniment of cholecystitis seems now to be generally admitted. Cholecystitis nearly always begins in the wall of the gall bladder and not in the mucous membrane. Any lesions which predispose to a hepatitis are likely to predispose to a cholecystitis. It is, therefore, not surprising that cholecystitis is often associated with the most frequent inflammatory lesions of the portal system, namely, appendicitis, peptic ulcer, typhoid fever and so forth. It is almost impossible to infect the mucous membrane of the gall bladder experimentally unless the cystic duct is ligated, the blood supply impaired, or trauma of the mucosa from foreign bodies occur. Disturbed function of an organ is one of the earliest manifestations of inflammation. Cholecystography is preëminently a functional-test of the gall bladder, and it does not necessarily reveal the most pathologic lesions. The two functions so far discovered are concentration of the contained bile and regulation of the pressure within the system of biliary ducts. A failure to obtain a visualization of the gall bladder does not signify an obstruction of the cystic duct. It may signify failure of power of concentration or disturbance of liver function to prevent excretion. The criteria upon which a diagnosis of cholecystitis shall be based include: (1) Stones; (2) adhesions; (3) thickening of gall-bladder wall and change of color; (4) enlargement of the "sentinel" gland of Lund; (5) hepatitis, and (6) cholesterol plaques seen in "strawberry" gall bladder. Seven hundred cases examined averaged 93 per cent of correct diagnosis. In several instances, it furnished positive evidence when clinical evidence was misleading. Experimental work carried on has demonstrated that the sodium salt of phenoltetraiodophthalein will allow simultaneous observations of the renal function, the hepatic function and of the condition of the gall bladder.

PATHOLOGY AND BACTERIOLOGY

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Chordoma: A Review, with Report of a New Sacrococcygeal Case.—A chordoma is usually a tumor of low malignancy, slowly infiltrating and tending to recur after removal. They occur chiefly in two places, corresponding to the anterior and posterior extremities of the notochord, for example, sphenoöccipital synchrondrosis and the sacrococcygeal regions. STEWART and MORIN (*J. Path. and Bact.*, 1926, **29**, 41) report a new case of the latter region and review the literature on the subject. Their case, a male aged 58 years, suffered from constipation for 5 years, a lump in the sacral region for 4 months, and some frequency of micturition for a few weeks. On admission a large inoperable tumor diagnosed chordoma and confirmed at biopsy was found. The operation wound discharged for some weeks with considerable reduction in the size of the tumor and amelioration of the symptoms. The patient is still alive in fairly good health $2\frac{3}{4}$ years later. Histologically, it was a chordoma of low malignancy. The authors find in all, 57 cases of chordoma. Twenty of them were of the sphenoöccipital group with an average age of 34.9 years. The sacrococcygeal group averaged 50.6 years. The former varied from 16 to 72 years, the latter from 22 to 68 years, with 36 males as compared to 15 females. The prognosis of the sphenoöccipital cases is death in 2.8 years from first appearance. In the sacrococcygeal group it is fatal in 6.4 years as an average. They vary as to the length of time between recurrences after removal. One case went as long as 5 years. One should separate the chordoma which is a true neoplasm of the notochord from the notochordal heteropiæ (ecchordosis physaliphora as the authors call them) which are really chordal ectopiæ. Twenty-four cases of these have been reported with an average age of 46 years. These generally consist of a soft transparent jelly-like nodule attached by a more or less slender pedicle to the middle of the dorsum sellæ. Chordomata vary in appearance according to their malignancy. Usually they are well encapsulated, and broken up into lobules by fibrous trabeculæ. Each lobule is composed of some transparent whitish or bluish gelatinous tissue, often with central areas of hemorrhage. They are locally destructive to bone, though widespread infiltration is rarely seen. Metastasis, so far confined to the sacrococcygeal cases, are even less frequent. Histologically the salient features are: (1) An alveolar type of growth; (2) the solid epithelial aspect of the younger and more cellular areas; (3) the cytoplasmic and intercellular vacuolation; (4) the formation intracellularly of a mucinous fluid which escapes from the cells and forms large seas of

mucin in which are left cellular islets. Minor points that have been noted are: The presence of intracellular glycogen, sometimes nuclear vacuolation, and occasionally mitotic figures. The treatment advised is operative removal when at all possible.

On the So-called Calcification in the Basal Ganglia of the Brain.—Aschoff in 1902 first referred to vascular calcification in the brain. Since then calcification affecting the vessels in the globus pallidus of the lenticular nucleus has been found repeatedly in patients dying from paralysis agitans and in encephalitis lethargica cases. HURST (*J. Path. and Bact.*, 1926, **29**, 67), however, has recently completed an examination of one hundred brains taken from various neuropathic cases. From his study it seems that a hemotoxylin-staining substance is present in the globus pallidus in a high proportion. In brief he divides his findings into three main groups: (*a*) Deposits in the vessels; (*b*) degeneration bodies; (*c*) fatty products of degeneration. Of the 100 cases examined, 50 per cent of them showed deposits of this hemotoxylin staining material in the vessels of the globus pallidus, particularly in its anterior half. This occurred in all age periods between twenty and eighty-one years, the greatest number in the 4th decade. In 5 of the 50 the veins also were affected. The deposits occur chiefly (1) in the media or (2) the adventitia and spreading to the media later. In cases of arteriosclerosis it may also occur in the intima. Degeneration bodies whose staining reactions were the same as the vascular deposits were found in 68 cases in the globus pallidus and in the putamen in 30 cases. Three varieties of these were described: (1) Spherical globules, minute points up to the size of a glial cell; (2) mulberry-shaped bodies, found also along the small vessels and apparently formed from aggregations of (1), (3) larger sized ones sometimes exceeding a nerve cell in size, these unlike the others were found most frequently in the lenticular nucleus. These degeneration bodies when lightly stained seem to show zones of paler staining. They rarely attain the size of a nerve cell while corpora amylacea are 2 to 4 times a nerve cell in size and the latter does not stain for iron or by Klotz's method. Fatty degeneration products: (1) In the globus pallidus alone stained for neutral fat and cholesterol; (2) a yellowish-brown lipoid found as deposits at times in the adventitia occasionally associated with the hemotoxylin-staining material. These deposits and degeneration bodies may stain brownish or brownish-purple with alum hemotoxylin and van Gieson's but usually deep blue black, with silver nitrate (von Kossa's method) brownish-black, Kotz's method black, Toluidine blue—blue. In all cases tried (10) they stained blue with the iron stain but after the action of hydrochloric acid or oxalic acid they stained brownish purple with alum hemotoxylin and van Gieson's and gave no iron reaction and no coloration by Klotz's method. Hence the author concludes that the process consists in the infiltration of one or more coats of the vessel with iron salts, the application of suitable tests failing to show the presence of calcium.

A Sacrococcygeal Chordoma.—Another fairly typical case of sacrococcygeal chordoma has been reported by ALEXANDER and STRUTHERS (*J. Path. and Bact.*, 1926, **29**, 61). A male, aged sixty-four years who had had lumbago occasionally for ten years, otherwise healthy, family

history clear. During the last eighteen months before admission he had had a swelling over the sacral region which increased to the size of a rugby ball. During the last month or two there was some difficulty in micturition and he was admitted because of acute retention. A portion of the tumor was removed. The wound discharged for six weeks during which time the tumor was reduced in size and the urinary function was restored following a temporary suprapubic cystostomy. Macroscopically the tumor resembled a colloid cancer, histologically it proved to be a chordoma, and many of the tumor cells showed nuclear vacuolation. The writers feel that in their case there is some evidence of a tuberculous focus being present in the tumor, either as a causative or secondary factor.

Experimental Intratracheal Injection of Bacillus Tuberculosis.—It is pointed out by BECKWITH and MILIZNER (*Am. Rev. Tuberc.*, 1926, **13**, 62) that the mucous membrane of the upper respiratory tract is the portal of entry for the tubercle bacilli, being conveyed to the lungs by various lymph channels, which are graphically illustrated by a chart. The authors aim to show that the usual mode of entry is by the tracheal route and that no local lesion will mark the point of invasion. Both human and bovine strains were used, which were purified by a careful technique of animal passage and then cultured on a special egg medium. A standard dose associated with India ink was inoculated just below the tracheal mucosa, through an open incision. The animals were killed at fourteenth to fifty-sixth-day intervals. The rabbits were negative in cultural and sectioning results but the guinea pigs illustrated the following important lesions: Early and extensive tracheobronchial gland involvement; few pulmonary evidences of disease; frequent and late splenic tubercles, and an early finding of tubercle bacilli in the cervical lymph nodes, without localized lesions. Traces of the India ink proved the invasion to follow along the lines of the lymph drainage. The finding of isolated lesions in the peribronchial lymphoid tissue is evidence that aspiration as the only mode of infection is not valid. Likewise the frequent but late involvement of the spleen can be explained on the basis of a blood infection after traversing the pulmonary lymphatics—all of which supports a lymphatic extension of the tuberculous infection, arising from a possible and very probable invasion through the trachea.

Pulmonary Hilum Tuberculosis in the Adult.—The unusual condition of tracheobronchial tuberculous involvement in adults is illustrated by a report of 9 cases given by FREED and WEBB (*Am. Rev. Tuberc.*, 1926, **13**, 37). The symptom complex in these cases differs from that found in the pulmonary form, and many of the diagnostic guides are wanting, but the following stressed by Hall are significant: Loss of weight; persistent daily fever; hemoptysis; cardiac pain; purulent expectoration, with the finding of a positive sputum, after repeated examinations, and that by the antiformin-concentration method. As only 3 out of the 9 cases showed an increase in the hilum shadow, these subsidiary signs of tracheobronchial thickening are important: Dyspnea, brassy cough, d'Espine's sign, and evidences of venous congestion. All laboratory assistance such as tuberculin tests, the Wildbolz auto-

urine reaction, red-cell sedimentation rate and a modified Lyon-Meltzer method of demonstrating tubercle bacilli are urged. The authors recommend the use of potassium iodid not only as a means to diagnosis but also to evacuate the superficial tuberculous glands. In conclusion a summary of the guides to diagnosis is given, the disease will be of the chronic type; without Roentgen ray evidence, apart from occasional thickening of the hilum; a localization in the lymph nodes, without involvement of pulmonary tissue; the finding of the tubercle bacilli and toxic manifestations similar to those of pulmonary tuberculosis.

Action of Unsaturated Fatty Acids on Tubercle Bacilli.—Boissevain (*Am. Rev. Tuberc.*, 1926, **13**, 84) follows up the work of those who have tried the action of fatty acids on tubercle bacilli, with this difference, that he found an associated dehydration unnecessary in the attenuation. The efficiency of the acid was shown to be dependent upon the degree of unsaturation, of solubility, the possession of a long carbon chain and a $-COOH$ group. Fulfilling these demands to the highest degree was linolenic acid, which succeeds in destroying the virulence of proven pathogenic strains after incubation periods as short as one hour. This reduction in virulence being proven by culture and animal inoculation. It was found that the soaps of fatty acids did not possess this attenuating power. However, as linolenic acid is highly absorbable by the tissues, it was thought that it would render the bacillus tuberculosis innocuous for animals, but this was proven to be unfounded and the explanation seems to be that in the buffered tissue fluids, soaps are formed and the fatty-acid effect is lost.

Tuberculosis of the Pleura.—By a study of the microscopic anatomy of the pleura Miller (*Am. Rev. Tuberc.*, 1926, **13**, 1) has adduced proof that phthisical pleurisy cannot be a primary disease. He shows that the localization, for the most part, is in the submesothelial layer, which is avascular and so the invasion is not hemotogenous but by extension from the pleural cavity or the lung. The author feels that the macrophages are the agents of this extension and that the complete history of invasion is a primary focus in the lung, then the bronchial lymph nodes with a final involvement of the pleura. The pleura is divided into four layers, the mesothelial, submesothelial, elastic and areolar. The first and third are so vascular as to remove the evidences of tuberculous inflammation and the elastic layer serves as a barrier to spread and so it is that tuberculous pleurisy clears up without forming adhesions unless the whole four layers are involved. The resistance of the pleura against destruction is evidenced by extensive cavitation with an intact pleural membrane.

Ependymomas of Lateral and Fourth Ventricles of Brain.—Hirsch and Elliott (*Am. J. Path.*, 1925, **1**, 627) report 2 cases of ependymoma of the brain; 1 primary in the lateral ventricle had the infiltrative qualities of a malignant tumor, while the other in the fourth ventricle was chiefly an expansile growth. This difference suggests that certain ependymomas may be benign, while others are malignant. The finding of blepharoplasten granules in the cells and of glial fibrils is considered necessary for the identification of tumors of ependymal origin in distinction to those arising from the choroid plexus epithelium.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Tuberculosis in the Tropics. A Review of Findings in 402 Autopsies Performed in Sao Paulo, Brazil.—LAMBERT and FILHO (*Am. Rev. Tuberc.*, 1925, **12**, 173) made a systematic study of the anatomic findings in 402 autopsies in Sao Paulo, Brazil, which revealed the following facts: Lethal tuberculosis was found in 83 cases, or 20.6 per cent; subsidiary tuberculosis in 15.4 per cent healed lesions only, in 4.5 per cent; and doubtful lesions only, chiefly instances of more or less extensive pleural adhesions, in 32.3 per cent. Assuming that half the doubtful lesions were tuberculous in origin, the percentage of cases showing evidence of active or healed infection was about 60 per cent. The percentage was practically the same for the second, third, fourth and fifth decades of life. The percentage of lethal tuberculosis in the negroes was almost double that in the whites, 27.3 and 15.5, respectively, whereas there were almost four times as many whites as negroes in which undoubted healed lesions were demonstrable. The anatomic character of the lesions, particularly among the whites, corresponds in general to that seen in the tuberculized peoples of Europe and North America, typical chronic pulmonary tuberculosis being the chief manifestation of the infection in a large majority of the cases. There is an apparent rarity of the bovine type of infection, perhaps accounted for by the custom of using only boiled milk. The high percentage of lethal tuberculosis in the series is probably considerably greater than would be found in a more truly representative group of cases, owing to the high mortality among the advanced cases admitted to the hospital from which the cadavers were obtained. It is believed, however, that the findings serve to emphasize the fact, generally recognized by the hygienists of the country, that tuberculosis, as in many of the countries of the temperate zone, constitutes one of the greatest scourges of this section of tropical America.

Syphilis in Relation to Pregnancy.—NATHANSON (*Surg., Gynec. and Obst.*, 1925, **41**, 320) states that in a series of 413 pregnant women, syphilis occurred in 2.90 per cent, which is in agreement with the incidence of 3 to 4 per cent reported by other investigators. The occurrence of a positive Wassermann reaction in pregnancy constitutes very decisive evidence of the existence of syphilis in the mother but does not necessarily mean that the child will develop syphilis. Routine micro-

scopic study of the placenta for evidences of Fränkel's disease affords more conclusive evidence as to the presence or absence of syphilis than does serological investigation. Syphilis is not an important factor in the production of abortions in the first trimester of pregnancy, and it has little influence on the incidence of miscarriages during the second trimester. It is, however, of predominating importance as the commonest and single cause of premature births and stillbirths in the last trimester of pregnancy.

Commercial Pasteurization.—In *U. S. Public Health Bulletin*, 1925, No. 147 is to be found a report prepared by a group of scientific workers on the efficiency of pasteurization as carried out commercially, using several different types of machines and varying the conditions, especially the temperature. It is pointed out in an editorial note that the Public Health Service does not seek to establish a standard definition for pasteurization, believing this to be best done by responsible local authorities. It is especially emphasized in the note that the efficiency of the pasteurizing machinery must be carefully scrutinized in order that all of the milk may be treated in the manner desired, and the Public Health Service unreservedly indorses pasteurization. From the point of view of the physician the important features in the summary and conclusions are: An examination of municipal and State milk laws shows that no single standard of temperature and time for the pasteurization of milk is as yet recognized. This is due to the fact that there is no single thermal death point for the tubercle bacillus and other pathogenic bacteria transmissible by milk, but there are many thermal death points depending on the time factor. From these numerous thermal death points and with differing consideration of a necessary margin of safety bacteriologists and health officials have made their independent selections and hence have arisen the variations in temperatures and times recommended as standards for pasteurization. The hemolytic streptococci used in these tests were destroyed by momentary heating by a commercial heater to 129° F. The diphtheria bacilli used in these tests were destroyed by momentary heating by a commercial heater to 129° F. The typhoid bacilli used were destroyed in the fourth series of tests by momentary heating by a commercial heater to 141° F., and by one type of commercial holder at 132° F. for thirty minutes. The bovine tubercle bacilli used were destroyed in some tests in three types of improved commercial pasteurizers at 138° F. for thirty minutes. These results are in harmony with the best laboratory determinations of the thermal death points of these species of bacteria. The recognition of a standard minimum temperature and time for the definition of pasteurization by health authorities is in the interest of public health, and such a standard should give first consideration to an adequate margin of safety above the temperature and time necessary for the destruction of tubercle bacilli. The temperature and time for pasteurization contained in the milk regulations of the cities of New York, Philadelphia, Baltimore and many other large cities, and the regulations of the State of New York, Connecticut, and other states, which is that "milk or cream shall be heated to a temperature of at least 142° F. and held at such temperature for thirty minutes or more,"

provides an adequate margin of safety, and is recommended as a proper standard for the definition of pasteurization by health authorities. This standard has been in use for some years with results satisfactory to the health authorities. In order to conform with this standard the industry must adjust the temperature of pasteurizing machines a degree or two above the minimum temperature of 142° F. to allow for fluctuations. This standard therefore requires that the pasteurizing machines shall be regulated so as to maintain an average temperature of from 143° F. to 144° F. Such a standard allows a minimum margin of safety for thirty minutes of 4° F. and an average margin of from 5° F. to 6° F. above the thermal death point of 138° F. for the tubercle bacillus. It is essential that proper emphasis be placed upon the words "heated" and "held" in the definition of pasteurization here recommended. Well-designed plants under competent operating supervision can be made to adhere closely to the standard minimum requirements. There are often, however, plants which are poorly designed and operated, especially the smaller plants, in which there are variations in both the temperature of heating and the time of holding which cannot be offset even by raising the minimum time and temperature limits. It is not the proper function of a statutory definition to attempt to establish limits based on such inefficient processes. The proper remedy for such variations consists in more competent supervision by public health officials and by all who are responsible for the operation of pasteurizing machinery.

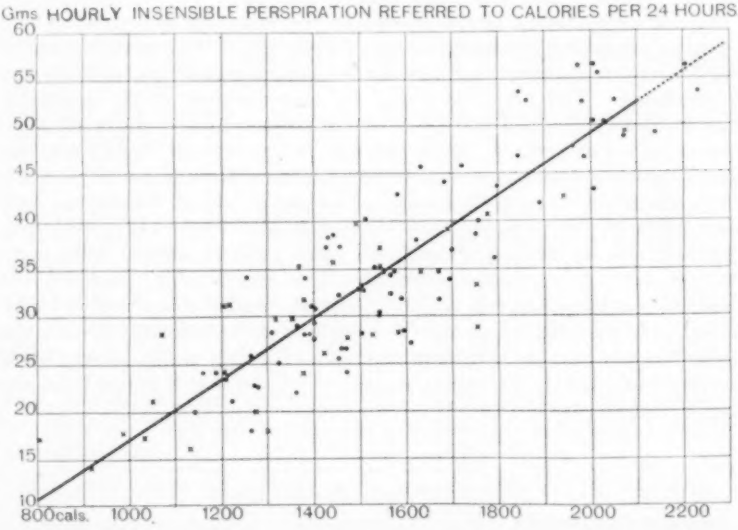
Immunization against Pneumonia.—Cecil (*Medicine*, 1925, **4**, 395) states that an attack of pneumonia confers on the patient a high immunity against the particular type of pneumococcus with which he has been infected. A small amount of cross-immunity is simultaneously established against the other types. By the injection of killed or living cultures of pneumococcus, it is possible to obtain an active immunity against the homologous type of pneumococcus. This immunity is evidenced in laboratory animals by the animal's resistance to infection and by the presence of various immune bodies in the circulating blood. Subcutaneous, intravenous, or intratracheal injections of pneumococcus vaccine produce in monkeys an active immunity against experimental pneumococcus pneumonia of homologous type. Pneumococcus vaccine when given in adequate doses confers immunity against pneumococcus pneumonia in man. The evidence in favor of such immunity rests on statistical studies and on the demonstration of immune bodies in the blood of those vaccinated. The chief indications for the use of pneumococcus vaccine at the present time are: First, to prevent recurrence in individuals who are highly susceptible to repeated attacks of lobar pneumonia. Second, for the prevention of outbreaks of pneumonia among fresh recruits in training camps. There is reason to believe that the recent isolation of certain derivatives of the pneumococcus which contain the antigenic principle will eliminate the undesirable features of vaccination against pneumonia and thereby render the procedure more practical in civil life.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

Perspiratio Insensibilis: Its Significance in Physiology and Pathology and its Relationship to Skin Temperature and Heat Loss.*—By FRANCIS G. BENEDICT (Director of the Nutrition Laboratory of the Carnegie Institution of Washington, Boston, Massachusetts). The



Relationship between the insensible perspiration per hour and the simultaneously measured heat production per twenty-four hours of a group of diabetic and thyroid patients. The diabetic patients are indicated by crosses, the thyroid patients by dots. The straight line curve representing the general trend of the points is suggested as a method for predicting probable metabolism from measured insensible perspiration.

early observations of Sanctorius on the "perspiratio insensibilis" have been followed by more recent studies with modern balances, and it has been found that the average man loses by insensible perspiration about 40 gm. per hour and the average woman somewhat less. Measurements over night, in which the individual is weighed just before retiring and again in the morning just after rising, on commercial scales sensitive to 10 gm., are sufficient for most purposes. Research work is best carried out with a delicate balance, capable of weighing an adult to within 0.1 gm. With this balance the experimental periods may be

* Abstract of a lecture given before the Physiological Society of Philadelphia, on March 15, 1926.

from twelve to fifteen minutes in length. The weighings at such intervals usually show that the insensible loss is regular from quarter hour to quarter hour and is in large part unaffected by wind velocity or indeed, removal of clothing. A large number of diabetics were studied at the clinic of Dr. Elliott P. Joslin at the New England Deaconess Hospital, Boston, by my associate, Dr. Howard F. Root, who found that if the hourly insensible loss is compared with the simultaneously measured metabolism the relationship between the two is very close. Similar studies were made with toxic-goiter patients from the clinic of Dr. F. H. Lahey of the New England Deaconess Hospital, and it was found that when the insensible loss per hour was charted against the measured metabolism of these diabetic and thyroid patients, a straight-line curve was obtained. Similar data for practically all the normal subjects studied also fell upon this straight-line curve. Hence the insensible perspiration or the insensible loss per hour is suggested as a means of predicting the metabolism. Obviously if the conditions under which the measurements are made are basal, the basal metabolism can be predicted. The practical use of the measurement of the insensible perspiration in a clinic has been demonstrated in a number of cases where the serious illness of the patient or, in certain highly nervous cases, a psychic disturbance has prevented the patient from coöperating in the metabolism measurements. The prediction of the metabolism from the insensible perspiration in such cases has changed the previously obtained false impression of metabolic status, and important deductions have thereby been made possible. The relationship between the insensible perspiration, the skin temperature, and the heat loss is found to be such that below an environmental temperature of 26° C. the insensible loss is extremely regular, but above this point, when visible perspiration appears, an excessive loss, chiefly of water vapor from the skin, is found.

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